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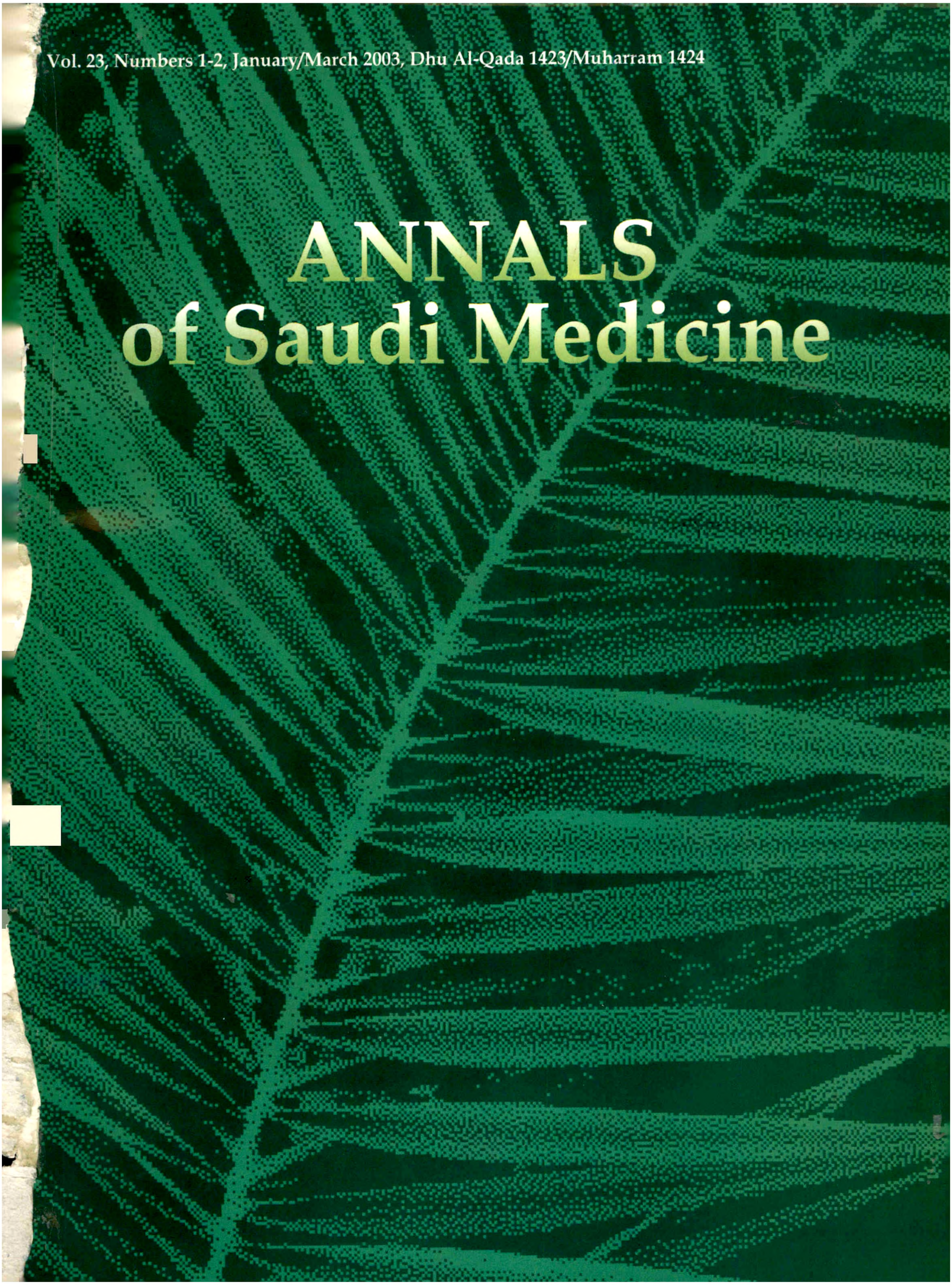

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Editorial

TEACHING MEDICAL ETHICS IN MEDICAL SCHOOLS

Fadheela Al-Mahroos, MD, FAAP; Raja C. Bandaranayake, MBBS, PhD, MSEd, FRACS

It has been well established that to practice "good medicine," doctors do not just need sound knowledge and skills but also the right attitude, conduct, and the ability to make difficult ethical decisions about the care of their patients. From time immemorial, doctors have always confronted ethical questions during their practice. In the present era, ethical dilemmas in medicine are widespread and complex, and touch the most sacred values of society. Decisions about medical ethics are no longer limited to medical professionals. Lay people, legislators, ethicists, theologians, politicians and policy makers, all play a role in influencing decisions taken in hospital wards.

New doctors swear the Hippocratic oath (or an equivalent professional statement) to adhere at all times to high standards of medical practice and ethics, and to protect the right of every patient to life, dignity, and confidentiality.[1] Yet, it is not certain how this oath is reflected in the curriculum of medical studies. The purpose of this report is to review the literature related to the teaching of bioethics in the undergraduate medical curriculum and to suggest some guidelines for its introduction in the Arabian Gulf countries.

History of Medical Ethics

The issue of medical ethics dates back to around 500 years BC, when the great Greek philosopher Plato expressed his deep concern about the inappropriate behavior of the doctor who acts "with the self confidence of a dictator," and who shows no respect or consideration for his patient's needs and feelings. He called for a code of ethics, which "makes a doctor a better healer," and thus laid the foundation for the core ethical values for doctors to practice good medicine. Among the earliest and most comprehensive statements on medical ethics in Islam is 'Adab al-Tabib' (the ethics of the physician), the work of Ishaq ibn Ali Al-Ruhavi who detailed the code of ethics required by any doctor. Al-Ruhavi emphasized the interrelationship between spiritual and bodily health: "The virtuous physician can improve both body and soul."[2]

Driven by the many perplexing medical ethical issues confronting physicians in Islamic culture, the first International Conference on Islamic Medicine adopted the Islamic Code of Medical Ethics which addressed the patient-doctor relationship, doctor-doctor relationship, professional secrecy, doctor's duty in wartime, responsibility and liability, the sanctity of human life, doctor and society, bio-technological advances, medical education and the oath of the doctor.[3]

In recent times, interest in teaching medical ethics took a major turn after the 1947 Nuremberg trials that uncovered the participation of some German doctors in the crimes committed against humanity during World War II. This raised the awareness about the importance of physicians' conduct and the need for the teaching of medical ethics to medical students.[4]

In the last 40 years, scientific advances in medicine, and the application of scientific methods in managing patients' problems have undoubtedly transformed medical practice and brought longevity and better life to mankind. Nonetheless, medicine has lost much of its humane aspects, and this conflict between technology and basic human values has led to the emergence of bioethics and an acceleration in the introduction of medical ethics courses in the curricula of medical schools throughout the world, especially in the US. Other forces for medical ethics education include the ethical dilemmas in the field of research, the rapid advances in human genome and genetic intervention, *in vitro* fertilization and, more recently, the issue of animal and human cloning. As well, improved access to information and the increased cost of medical care have contributed to this dilemma. The recent emergence of managed care and market forces in the US represented a major challenge to the medical profession. Physicians found themselves obliged to meet the demands of third-party payers in making decisions, which were not necessarily the best to meet their patient's needs.

Concept of Medical Ethics

The concept of medical ethics is broad and not easy to define. Extensive debate exists in the literature about which ethical theories or ethical principles or values pertaining to the standard of medical practice should be adopted. A discussion of the different views is beyond the scope of this review.

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Concern about medical ethics education and practice is worldwide. However, the best documentation in the literature about the trend in medical ethics education is from the United States and the United Kingdom. Most hospitals in the United States and in many other countries, have ethics committees (usually mandated by accreditation agencies), made up of lawyers, social scientists, theologians, philosophers and physicians.[3] Medical ethics teaching in the United States started as simple isolated courses concentrated in the pre-clinical stage. The first started at the Milson S. Hershy Medical Center in Pennsylvania in 1967, but the various ethical issues facing the profession and the public outcry for ethical standards in the practice of medicine led to changes in medical school curricula and the introduction of structured medical ethics courses, a trend which has continued to date. Recently, the AMA's Institute for Ethics developed an online course in Physician Ethics and Professionalism, based on the AMA "Code of Medical Ethics."

In the UK, medical ethics teaching has been increasing since 1987.[4] However, it escalated rapidly in 1993, when the General Medical Council (GMC), in an attempt to reform medical education, formulated its recommendations on undergraduate medical education.[5] In 1998, a Consensus Group of Teachers of Medical Ethics and Law in UK Medical Schools formulated a consensus statement about teaching medical ethics and law within medical education and proposed it as a model for the UK Core Curriculum in medical ethics. It included 12 themes: informed consent and refusal of treatment, the clinical relationship: truthfulness, trust and good communication, confidentiality, medical research, human reproduction, the new genetics, children, mental disorders and disabilities, life, death, dying and killing, vulnerabilities created by the duties of doctors and medical students, resource allocation and rights.[6] In many countries, the integration of medical ethics into the formal curriculum has become the standard. A study by Miyasaka et al. in an international survey of medical ethics in 13 Asian and Oceanic countries reported that 89% of medical schools had some courses in medical ethics.[7]

In the Arabian Gulf University, medical ethics is taught in the pre-medical year as part of the subject "Islam". In the following pre-clinical and clinical years, there are no systematic medical ethics courses or structured integration in the curriculum, except for a vertically integrated pre-clinical course in communication skills, which combines cognitive and practical skills.[8] Similarly, a recent report from Saudi Arabia indicated that medical ethics education is lacking in some Saudi Medical Colleges.[9]

It is obvious that the need for medical ethics education is recognized in most countries and has become a component of undergraduate formal medical training in most medical schools. Most ethical problems faced physicians throughout the world are similar, with some unique issues pertinent to some countries. The teaching of medical ethics has been given high publicity in two recent international initiatives, which have laid down standards and global essential requirements in medical education.[10,11]

Course Content

While most disciplines in medical education are expanding and changing, they have clear boundaries. Medical ethics on the other hand, is evolving fast and becoming more complex, with many stakeholders who have influence on the discipline. The unifying theme is "the centrality of values and ethics in medical education and the importance of the humanities for dealing with them responsively and responsibly."[2] One of the recommendations for medical ethics content was proposed at the De Camp Conference[12] of medical ethics teachers in the US. It included the ability to identify the moral aspects of medical practice: the ability to obtain valid consent or refusal of treatment, the knowledge of how to proceed if a patient is only partially competent, fully incompetent, or refuses treatment; the ability to decide when it is morally justifiable to withhold information from a patient, or to breach confidentiality; and the knowledge of the moral aspects of caring for a patient whose prognosis is poor.

At Stanford University School of Medicine in California, bioethics is taught as a "vertical thread" throughout the undergraduate medical school curriculum. At John Hopkins University School of Medicine the curriculum comprises diverse elements such as bioethics, history of medicine, art, spirituality and medicine, economics, multicultural issues, and law.[13]

At the Bristol Medical School in the UK, medical ethics teaching received a considerable push by the establishment of the Center for Ethics in Medicine in 1997. Brennan [14] summarized the key points of the Bristol Medical School approach in teaching medical ethics as follows: the teaching is student-centered; the content is patient-centered; the course is structured, vertical and incremental; it is case-based and grounded in theory but applied to clinical practice, the approach is inclusive and humanistic; team-teaching is applied whenever appropriate; the sessions are interactive, non-didactic and conducted in small and large groups, with opportunity given for discussion within a safe environment; positive critique is employed throughout.

Teaching Medical Ethics in Medical Schools

The medical school setting represents an ideal place for laying the foundation for professionalism and medical ethics through integration with various subjects in the pre-clinical stage and during clerkships. Teaching medical ethics is expected to improve patient care and patient and professional satisfaction with improved quality of care. Studies are needed to validate many of these assumptions.

Teaching medical ethics will sensitize students and increase their awareness and hopefully, it will lower the threshold of tolerance to the inhumane treatment of patients. It might help to "rehumanize" medicine, ensure that future physician will be a caring and compassionate person who respects the patient's dignity and privacy, and believes that patients are entitled to be told the truth, to participate in decision-making, and most importantly, live and die in dignity.

Over-expectations represent a real challenge. It is unrealistic to expect medical ethics education to be a "pedagogical panacea" for medical dilemmas.[2] Although medical ethics education aims to sensitize students to ethical issues and to provide the knowledge necessary for morally sound judgment, it will not turn every student into a humane, sensitive and compassionate doctor. Those with personality problems or who are inherently rude are least likely to change. It may not change "students' values and beliefs, or ensure ethical conduct."[15] It is the job of medical school admission bodies to function as gate-keeper, to ensure, as much as possible, that the students entering medical schools possess the personal traits and characteristics which meet the expectations of the profession and the society from a doctor. In addition, regardless of what the official curriculum aims and content are, the "hidden curriculum"[15] and the institutional culture have a significant influence on the students and determine their attitudes. Undoubtedly, any contemplated change cannot succeed if these aspects are not addressed.

Barriers

One of the major hurdles to successful implementation of medical ethics courses is unsupportive institutional culture. As Kenneth Ludmerer states, "an unfriendly institutional culture can easily undermine the well-intentioned efforts of those trying to impart professionalism through the means of curriculum."[16] This institutional culture could be a lack of interest and disregard for the importance of teaching medical ethics, improper bedside manners of the teacher and the poor treatment and humiliation of students and residents. Employing a change strategy through faculty involvement and education would be necessary. It would also help to include medical ethics in faculty development programs.

One of the challenges to implementing medical ethics courses is the demand on curriculum time and the ability to accommodate them in the face of an ever-expanding curriculum content. There is no easy solution to this problem. However, the need for medical ethics education is so persuasive that it should be integrated horizontally and vertically within the curriculum, employing different teaching methods.

Another challenge is agreeing on the syllabus content. It is unusual to disagree about the course content of acute pneumonia, but it will be difficult to get a group of medical ethicists or physicians to agree about a uniform syllabus in medical ethics. The UK Consensus Group statement represents an exception.[7] Many of the ethical dilemmas facing doctors do not have a clear correct and wrong answer. Thus, medical ethics courses should aim to teach a set of well-established principles which the future doctors can apply to different settings and circumstances, and to inculcate in the student the attitude of considering both sides of the coin when faced with an ethical dilemma.

Efforts to introduce medical ethics courses can be met with a great deal of resistance for different reasons. To some, ethical problems in medicine seldom arise, and when they do, it is obvious that what should be done is "trivial." To some, ethics is taught, not as a formal course but on ward rounds in the context of discussing individual patients (redundant). To others, there are no right or wrong answers with regard to ethical issues, and, therefore, ethics is about attitudes and moral character and not amenable to teaching the impossible.[6] Another difficulty is the skepticism about teaching others to be compassionate through courses.

Guidelines for Implementation in Arabian Gulf Colleges of Medicine

Recognition of the Need for Medical Ethics Education

Open and transparent discussion throughout the institution, including faculty and students, about the rationale for the change, to try to reach a consensus about the need for medical ethics education is crucial. A survey to identify the needs and perceptions of faculty and students about medical ethics education might be a good starting point. If a goal of the institution is "to promote humanistic values as the basis of medical practice," it is implicit that students should acquire a knowledge and understanding of "ethical and legal issues relevant to the practice of medicine" and an "ability to understand and analyze ethical problems so as to enable patients, their families, society and the doctor to have proper regard to such problems in reaching decisions."[5]

Curriculum Design and Course Content

There is no consensus on what makes a well-rounded curriculum in clinical bioethics. Much variety exists in what is taught, how, when and by whom. The most elaborate core curriculum, which can be adopted and adapted for each college, is that proposed by the recent UK Consensus Statement, which included the 12 themes.[6]

When medical ethics education was first introduced, the method of education was mainly in the form of didactic courses. It was soon recognized that formal courses alone would not reshape human behavior and attitudes, and schools adopted different methods. In addition to didactic teaching in large groups, small groups discussion and problem-based teaching, students need role models. At the University of Chicago, teaching of medical ethics is based on six principles: clinically-based, case-based, continuously reinforced in class, coordinated with clinical clerkships, cognitive training in the fundamentals of ethics, and clinicians functioning as instructors and role models.[15] Clinical relevance and meeting the needs of the community are other considerations in whatever teaching method is adopted. According to the UK Consensus Statement; it should begin early and be reinforced throughout the course. Sufficient curriculum time and resources should be explicitly allocated to its teaching.[17]

Responsibility for Teaching Medical Ethics

Schools differ in this respect. In the beginning the subject was taught by either a physician with interest in ethics or by an ethicist with or without clinical experience. In either case, it should be taught by those who do it well and who have the capacity to motivate students. Most importantly students need teachers who are good role models, who practice what they preach in their interactions with patients, students and colleagues. The UK Consensus Statement proposed that the teaching of this subject be widely shared within medical schools, but "its adequate provision and coordination requires at least one full-time senior academic in ethics and law with relevant professional and academic expertise."[17]

Assessment of Educational Outcome

Despite the fact that ethics education is offered throughout the world, there is no evidence that such education has influenced the attitude and behavior of doctors, or improved patient-doctor relationships and the outcome of patient care. On the contrary, the image of doctors (real or perceived) is deteriorating, and physicians are increasingly seen as greedy, insensitive, and providing impersonal care. Kass summed this up recently, in a critical look at medical ethics education in the US, that "though originally intended to improve our deeds, the practice of ethics, if truth be told, has at best improved our speech."[21]

There is a pressing need for well-structured research to identify: first, why the good intentions of imparting medical ethics and professionalism on medical school graduates do not seem to be fruitful or tangible; second, what the intended learning outcomes of medical ethics courses are; and third, how we will assess and measure the impact of the course on doctors' behavior, patient care and satisfaction. The UK Consensus Group recommended that assessment of medical ethics should be formal, as are all other core subjects within the curriculum, and should have the same importance as assessment in any other core subject. "Without such assessment, ethics and law applied to medicine cannot be taught successfully within the medical schools. The teaching itself should also be assessed in the same way as is teaching in other core subjects."[18]

Conclusions

The rapid advancement in scientific technology and the phenomenal expansion in knowledge have posed several ethical dilemmas, which doctors are required to deal with. In addition, despite all the scientific advancement and improvement in medical care, medicine cannot achieve miraculous cures and avoid the inevitable. The physician can, however, provide comfort and empathy, which are essential skills for every physician.

Public dissatisfaction with doctors is rampant with patients complaining that doctors are careless, impersonal, greedy, and unethical. Recapturing the doctor's trustworthiness is a pre-requisite for establishing a healthy patient-doctor relationship. Inculcating ethical values in medical students improves the quality of patient care, in terms of both the process and outcome of care, patient-doctor relationships and patient satisfaction with the process of care. The best time to implant the seeds of medical ethics is in the undergraduate stage when the students are receptive and not overwhelmed by the daily demands and stresses of postgraduate training. Identifying why we need medical ethics education is important to convince all stakeholders to introduce it in the curriculum. Identifying the goals and aims of medical ethics education will clarify the expected outcomes and what will be assessed. The content of the course should be relevant to the culture and based on societal needs, while the accumulated international experience should be taken advantage of. Methods of teaching need to be variable and integrated throughout the curriculum. Introducing this vital change mandates both human resources and curriculum time. Most importantly, however, the medical student must be exposed to role models who practice ethical medicine. "The innovation of teaching human values and ethics is not simply a transient pedagogical fashion. It is a recognition that the physician as scientist and the physician as humanist must converge if medicine is to be a boon and not a threat to individuals and society."[2]

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COMPLETENESS AND VALIDITY OF CANCER REGISTRATION IN A MAJOR PUBLIC REFERRAL HOSPITAL IN SAUDI ARABIA

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Background: The 1994 Saudi National Cancer Registry (NCR), a population-based registry, showed a crude incidence rate (CIR) of 39/100,000 for all cancers in the Saudi population. The low CIR suggested possible under-reporting, especially during the early years of operation. This study was aimed at estimating the number of missed cases due to under-reporting, and to assess the validity of reported data from a major public referral hospital in Riyadh city.

Materials and Methods: We compared cancer cases from three data sources: medical records (MR), which were the original source of NCR cases; pathology reports (PR); and death certificates (DC). We estimated the missing cancer cases using the capture-recapture method with log-linear models of Fienberg to correct for interdependency between the three data sources. To assess the validity of the data, we reabstracted records of about 8% (39/476) of previously reported cases from the same hospital.

Results: A total of 811 cancer cases were reported through the three sources, i.e., MR 611 (75.3%), PR 639 (78.8%) and DC 204 (25.2%). After fitting a series of log-linear models to the three sources of data, the three sources were found to be statistically dependent. Capture-recapture method indicated that 384 cases were missed, giving an estimation of 1195 cancer cases to be reported. Using these 1195 estimated cases; the estimated ascertainment rates were 51% for medical records, 53% for pathology reports, 17% for death certificates, and 68% for the aggregated registry. In the validity assessment, major disagreement between the abstracted and reabstracted data was found to be highest for stage of disease (44%), followed by histology code and behavior (25.6%). Minor disagreements were most common for date of diagnosis (36%) and grade (36%). Overall, agreements were highest for laterality (95%), followed by primary site codes (90%) and basis of diagnosis (85%). Agreement of tumor description variables (site, histology, behavior, and stage) was 57%.

Conclusion: Cancer registration will require substantial improvements in both completeness of reporting and data quality at the hospital level. Use of multiple data sources and estimation of missed cases will help ensure completeness of case registration.
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Key Words: Cancer Registry, capture-recapture method, completeness, validity.

Disease registries are important in measuring the incidence and prevalence of a disease as well as to study its natural history. For instance, cancer registry is essential for a national cancer control program.[1] Its primary function is to document and maintain all cancer cases occurring in a defined population in which the personal particulars of cancer patients and the clinical and pathological characteristics of the cancers, are collected continuously and systematically from various data sources. Such information is the primary resource not only for epidemiological research on cancer determinants, but also for planning and evaluating health services for the prevention, diagnosis and treatment of the disease.[2] Quality control of registered data is essential especially when several routine case-finding procedures, such as pathology and autopsy reports, hospital patient disease information systems, radiotherapy notes, and death certificates are used. The Saudi National Cancer Registry (NCR) is a population-based registry that was established in 1992 under the Ministry of Health (MOH). It covers approximately 18 million Saudi and non-Saudi residents.[3] A ministerial decree has rendered cancer a mandatory reportable disease, with accessibility of data to all MOH, governmental and private hospitals, clinics, and laboratories throughout the Kingdom. The reporting of cancer cases to the NCR from Saudi Arabia started in January 1994. The 1994 report showed a crude incidence rate (CIR) among the Saudi

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population to be 39/100,000, with a male-to-female ratio of 1.2:1.[3] Almost all cases (95.0%) were diagnosed microscopically.[3]

Completeness of registration may be defined as the extent to which all incident cancers occurring in a target population are included in the registry database. Evaluation of completeness in a cancer registry depends on the number of data sources available. The rationale is that fewer cases will escape the net, and that the quality of data will be enhanced by bringing together all items related to patients in a single file.[4] The higher the average number of sources per case, the higher the degree of completeness of the registration process.[5]

The capture-recapture methodology, originally developed for estimating demographic parameters of animal populations has been applied to human populations.[6-8] The purpose of using the capture-recapture model is the ascertainment of data for estimating the size of a target population based on several incomplete lists of individuals. Another essential component in evaluating the quality of data of registries is to evaluate their validity.[5]

Cancer registries exist in many parts of the world, but relatively little systematic work has been done to evaluate the quality assurance of registered cases. This study was designed to identify missed cancer cases through different sources of case finding in a major public referral hospital in Riyadh, to estimate the rate of under-registration and to evaluate the completeness of the cancer registry, as well as assess the validity of reported data.

MATERIALS AND METHODS

Completeness

More than 20,000 pathological reports and 1030 death certificates from the Statistics department (Ministry of Health) that were reported during 1994 were reviewed manually. Unmatched cases for medical records number with pathology report and/or death certificate registry were further investigated to ensure cancer diagnoses during 1994. Unfortunately patients who were diagnosed and treated at outpatient clinics with positive pathology results were not reported because they had no medical records. We excluded positive outpatient cancer cases because of incomplete information. Therefore, completeness and validity of the records applied to inpatients only.

Validity

We selected 39/476 (8.2%) cases at random to assess the validity of data abstracted and reported by the Tumor Registry at King Faisal Specialist Hospital and Research Center (KFSH&RC). Information was reabstracted directly from patients' medical records into the standard National Cancer Registry (NCR) registration form. Coding was performed by a certified tumor registrar and then entered using the original NCR data entry format. Epi-Info software program was used to check for inconsistency of data that had already been reported. Results were summarized and analyzed using major and minor disagreements for selected key data items developed by the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute and the Centralized Cancer Patient Data System (CCPDS, 1985) (Table 1). The SPSS software was used for fitting series of log-linear models to the data, and chi-squared tests were calculated to assess source dependency as could be judged by the interaction term of the fitted model. The final model was used to calculate the missing cell (Table 2).

TABLE 1. *Major and minor disagreements for selected key data items (CCPDS, 1985).*

Item	Code	Major disagreements	Minor disagreements
Date of diagnosis	Month and year	Different calendar year Difference >1 month	Difference <1 month
Primary site	4 digit (ICD-O**)	Difference in first 3 digits	Difference in 4th digit only
Behavior	IDD-O	Any difference	–
Grade	ICD-O	–	Any difference
Basis of diagnosis	–	Histologically confirmed vs. non-histologically confirmed or death certificate only	Difference between histological or non-histological diagnosis
Stage	–	Difference resulting in change of summary stage	Any difference
Laterality	–	–	Any difference

*Developed by Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute and the Centralized Cancer Patient Data System (CCPDS, 1985); **ICD-O=International Classification for Diseases-Oncology edition.

TABLE 2. *Frequency of the cancer cases which was ascertained by the three sources.*

		Death certificates	
Medical records	Pathology reports	Yes	No
Yes	Yes	89	423
	No	33	66
No	Yes	9	118
	No	73	x

X=estimated by log-linear model to be 384 (95% confidence interval 166-898).

TABLE 3. *Distribution of cancer cases by source of data.*

Sources of case finding	No. of cases (%)
Death certificate (DC) only	73 (9)
Pathology laboratory (PL) only	118 (14.5)
Medical records (MD) only	66 (8.1)
DC+PL	9 (1.1)
DC+MD	33 (4.1)
PL+MD	423 (52.2)
DC+MD+PL	89 (11)
Total	811 (100)

Results

During 1994, only 611 incidence cancer cases were reported by KFSH&RC to the NCR main office. After data cleaning at the NCR main office, only 476 cancer cases

TABLE 4. *Results of the major, minor and overall disagreements of reabstracted cancer cases for the selected key data items.*

Item	Major disagreements n=39(%)	Minor disagreements n=39(%)	Overall disagreements n=39(%)	*P*-value
Date of diagnosis	9 (23.1)	14 (35.9)	16 (41)	<0.001
Primary site	4 (10.3)	0 (0)	35 (89.7)	0.129
Behavior	10 (25.6)	0 (0)	29 (74.4)	<0.001
Grade	0 (0)	14 (35.9)	25 (64.1)	<0.001
Basis of diagnosis	6 (15.4)	0 (0)	33 (84.6)	<0.05
Stage	17 (43.6)	0 (0)	22 (57.4)	<0.001
Laterality	0 (0)	2 (5.1)	37 (94.9)	0.587

**P*-values correspond to the exact binomial test comparing the sample proportions with 0.95.

were attributed to the same hospital whereas the remaining cases were referred from other different hospitals in different regional offices. Active case finding identified 811 newly diagnosed cancer cases through the three sources of data collection, i.e., medical records, pathology reports and death certificate registry (Table 3), as compared with 611 cases that were reported by the tumor registrars from medical records only. We were able to identify 745 (91.9%) cases through pathology reports and death certificate registry. Of these, 639 (78.8%) cases were found to have pathological reports, and 204 (25.2%) cases had death certificate reports. After matching cases reported by active case finding with cases reported by medical records, we were able to identify 200 (24.7%) cases that were not reported by tumor registrars. Of 222 death certificates diagnosing cancer as cause of death, 18 (8%) were excluded as they were found not to be cancer cases.

By fitting a series of log-linear modeling to the three sources of data (Table 2), we found that all three sources were statistically dependent. We calculated the number of missed cases from the three sources to be 384 (95% confidence interval 166-898), giving an estimation of total cancer cases of 1195. Using the estimated figure of 1195, the estimated ascertainment rates were 51% for medical records, 53% for pathology reports, 17% for death certificates, and 67% for the aggregated registry.

Estimation of Validity

Analyses were made for 39/476 records (8.2%) during 1994. Major disagreement about the abstracted and reabstracted data was found to be highest for stage of disease (43.6%), followed by histology code and behavior (25.6%), whereas minor disagreement found to be highest for date of diagnosis (35.9%) and grade (35.9%). Overall, agreements were highest for laterality (94.9%), followed by primary site codes (89.7%) and basis of diagnosis (84.6%), while date of diagnosis and stage had the lowest agreement percentage (Table 4). Agreement of tumor description variables (site, histology, behavior, and stage) was 57.4%. Patients' demographic variables were not analyzed because the data were not standardized.

Discussion

In practice, no registry can achieve 100% completeness; there will always be some omissions for various reasons.[12] Robles et al. (1988) used the capture-recapture method to estimate completeness of the Ontario Cancer Registry (Canada), and found completeness rate to be about 93%.[13] Although outpatient cancer cases were not included in this study, almost 25% of cancer cases in 1994 were not identified. Tumor data were collected solely from one source, the medical record, despite the fact that the hospital medical record system was not up-to-date. In addition, during the first years of nationwide cancer registration, registry staff were mostly inexperienced. This study provides strong need for collecting from multiple sources in order to include all possible cancer patients seen or diagnosed at health care institutions. The proportion of completeness increased by 17% when the three sources were used as compared to only one source of data (68% completeness of aggregated sources versus 51% for medical records only). This would have been further increased if we had included missed outpatient cases. Degree of completeness of the registration process is directly proportionate with the number of data sources. The higher the number of data sources, the higher the likelihood of completeness.

Ninety-five percent of the total reported cancer cases to the NCR had histopathological diagnosis during 1994. In this study, 9% of cancer cases were identified through death certificates only, which were not checked by tumor registrars. Countries with long experience in tumor registration such as Sweden and Denmark have reported 4.5% and 8% cancer cases, respectively, through death certificates only.[9] Therefore, access to death certificates is very important both to enhance completeness of data collection and to evaluate the degree of completeness achieved.

The capture-recapture methods offer the potential to reduce the cost of disease registers, and to reduce bias in the estimation of incidence and comparison of population groups using proper modeling that adjust for dependency between different data sources. In this study, estimated missed cases were 1.5 times higher (1195 cases) than those identified by active case finding from the three sources (811 cases) and almost twice the number that has been reported by the tumor registrars. This indicates the importance of regular quality control of registered data, especially when several routine case-finding procedures can be used.

Due to incomplete information in patient files, we limited the reabstracted record method to a few key items, mainly to those with coding system. A lot of demographic data were not included due to the inconsistencies in translating Arabic written names into English. Epi-Info and other software programs are unable to overcome this problem. Our results of validity evaluation showed high proportions of major, minor, and overall disagreements as compared to other studies in different countries.[5] In 1976, West selected about 20% of the registrations in the South Wales Cancer Registry (UK) for the year 1972, and found that 5% of cases had been coded to incorrect diagnosis and 13.6% had incorrect year of diagnosis.[14] In 1988, Fulton et al. reabstracted 280 cancer cases registered in Rhode Island Cancer Registry, and found major disagreement of 5.4% for primary sites, 16.1% for stage, and 9.6% for histology.[15] In 1993, Schouten et al. compared abstracted data by 20 clinicians, with the cancer registry records in the Netherlands, and found major disagreements of 6% for primary cancer site, 2% for histopathological type, and 2% for behavior code.[16] The higher proportions of disagreements shown in this study may be explained by lack of experience, as it was the first operational year for the NCR. Also, the existing computer software used by the NCR has limitations in checking for data quality at the time of data entry. This means that impossible and incorrect but logical codes and combinations of codes for different variables in the same case record may occur. Adopting more advanced computer software readily available in the market can solve this problem. One such program has been developed and used by the International Agency for Research on Cancer (IARC, Can-Reg software), World Health Organization.

Conclusion

Cancer registration will require substantial improvements in both completeness of reporting and data quality at the hospital level. Use of multiple data sources and estimation of missed cases will help ensure completeness of case registration.

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HISTOLOGICAL AND HISTOCHEMICAL ALTERATIONS IN THE KIDNEY INDUCED BY LEAD

Bashir M. Jarrar, PhD

Background: Although lead intoxication is one of the most common forms of metal intoxication, the histochemical alterations in the renal tissues due to chronic lead exposure is limited and has not yet been well identified.
Subjects and Methods: A total of 60 male Wistar albino rats (*Rattus norvegicus*) were exposed to lead acetate trihydrate (0.0, 0. 25, 0.5, 1.0 and 2% for 1 to 12 months) in drinking water to investigate the histological and histochemical alterations in the renal tissues due to lead.
Results: Chronic exposure to subtoxic doses of lead produced distinct progressive tubular, glomerular and interstitial damages. Tubular changes occurred earlier than glomerular and interstitial ones, and included anisokaryosis, nuclear pyknosis, karyomeglay, development of intranuclear and cytoplasmic inclusions together with tubular dilation, necrosis, vacuolization, tubular hyperplasia and solid tubular adenoma. The glomerular alterations were mainly mesangial hypercellularity, segmental proliferation, focal and segmental glomerulosclerosis, glomerular hyalinization and glomerular tuft alterations.
Conclusions: The findings indicate that lead produces significant histological and histochemical changes in the kidney that lead to severe complications.
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Key Words: Lead, kidney, intoxication, histology, histochemistry.

Lead intoxication is probably the most common form of heavy metal intoxication,[1-3] and is well documented as one of the most dangerous and insidious poisons to man.[4-5] The absorbed lead is conjugated in the liver and is passed to the kidney, where a small quantity is excreted and the rest accumulates in and interferes with the function of body organs, especially the kidney as a target site for lead toxicity.[6-9] Continuous environmental and occupational lead exposure can lead to chronic nephropathy,[6,10,11] which is a characteristic manifestation of lead toxicity and characterized by tubular, interstitial and glomerular damages, including renal lesions, tumors and cancer risk.[12-15] The long-term effects of lead chronic exposure have been documented by several investigations with special attention to the exposure of developing animals and young children.[6,16-20]

The histochemical alterations in the renal tissues due to chronic lead exposure is limited and have not yet been well identified. With this objective, a detailed histological and histochemical studies were undertaken on the kidney of Wistar albino rats killed at one month intervals up to 12 months after lead acetate trihydrate treatment.

Subjects and Methods

A total of 60 male Wistar albino rats (*Rattus norvegicus*) of the same age weighing 110-130 g of King Saud University colony were used. Animals were randomly divided into five groups of 12 rats each. Following a period of stabilization (7 days), lead acetate trihydrate was administered in drinking water at the rate of 0.0%, 0.25%, 0.5%, 1.0% and 2% (Proanalysis-Merk, Germany). The control group received 2% sodium acetate in the drinking water and all groups were maintained on standard laboratory animal diet pellets. One animal from each group was killed by dislocation of the neck at intervals of one month during 12 months of treatment with lead acetate trihydrate.

Fresh portions of both kidneys from each rat were cut out rapidly, fixed in neutral buffered formalin (10%) and Gendre's fluid and then dehydrated, with grades of ethanol (70%, 80%, 90%, 95% and 100%). Dehydration was then followed by clearing the samples in two changes of chloroform before being impregnated with two changes of molten paraffin wax, embedded and blocked out. Sections (4-5 µm) were stained according to Pearse,[21] Drury et al.,[22] Bancroft and Stevens,[23] and Kiernan[24] conventional histological and histochemical stains.

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Results

Tubular Alterations

Lead acetate trihydrate produced alterations in the tubules, glomeruli and interstitium in the kidneys of lead-treated rats. These changes appeared early in the form of nuclear and cytoplasmic pleomorphism, particularily in the proximal convoluted tubules.

Nuclear alterations included anisokaryosis, nuclear pyknosis, karyomegaly, development of intranuclear and cytoplasmic inclusion bodies and frequent mitosis. These changes were seen in all lead-treated rats from one month and onwards. Anisokaryosis was one of the early alterations where a considerable proportion of proximal tubular cells contained enlarged nuclei while others appeared normal. Some epithelium lining cells of the proximal tubules also has developed pyknosis. Intranuclear inclusion bodies were developed in the nuclei of some epithelial cells of the proximal tubules (Figure 1). In the beginning of lead exposure, the inclusion bodies were small but their frequency and sizes increased with the duration of exposure to lead up to 12 months, while this frequency was decreased in the proximal tubules of kidneys which developed intertubular fibrosis.

Cytoplasmic changes were mainly seen in the form of cytomegaly and development of cytoplasmic inclusions. Some cells of the proximal tubules, especially those with intranuclear inclusion bodies were enlarged with cell-to-cell variation in size and shape and showed tubular cell unrest. This alteration was first observed in the inner edge of the cortex and progressed into the remaining cortex with the higher doses and duration of lead exposure. The number of the enlarged cells was also increased with increasing the dose and duration of lead exposure. Some cells of the proximal convoluted tubules were irregularly occupied with small crystalline bodies which have locally coalesced and occasionally protruded into the tubular lumen. These cytoplasmic inclusions were stained positively with ninhydrin-Shiff, Timm sulfide-silver and rhodizonate techniques. Also, these inclusions responded positively with Schmorl reaction, nile blue sulfate, toluidine blue, osmium tetroxide and, to a lesser extent by oil red O and Sudan black B stains but reacted negatively to Feulgen reaction, nile blue and alizarin red techniques.

Tubular damages also included degeneration, swelling, dilation, vacuolation, thickening of the tubular basement membranes and epithelial necrosis. These alterations appeared early with high doses of lead acetate trihydrate at 2% for 4 months and more of treatment. Focal tubular damage was seen at 0.5% for 5 months of exposure while isolated tubular damage was observed at 2% for 3 months and more of exposure. Many tubules showed dilation mainly in the pars recta and some dilated tubules contained densely eosinophilic (colloid) casts stained positively with PAS but responded negatively to Best's carmine and alcian blue techniques. Cystically dilated proximal tubules were also demonstrated together with thickening and accentuation of tubular basement membranes (Figure 2). Tubular atrophy first appeared at 5 months with some increase in severity thereafter.

Focal cellular necrosis was observed in some of the renal proximal tubules of lead-treated rats. The necrotic tubules showed thinning or absence of the proximal tubular brush border at 2% of lead acetate trihydrate. Vacuolar degeneration was observed mainly in the distal segment of the proximal tubules, while tubular vacuolation was seen in all treated rats up to 3 months of lead exposure but became rare thereafter.

Glomerular Alterations

Glomeruli in rats which received 1% lead acetate trihydrate or less for seven months or less were free from any significant alterations or proliferative changes. By then, alterations in the glomeruli of lead-treated rats started to appear in the form of mesangial hypercellularity, sclerotic changes, segmental mesangial proliferation and occasional increase in the Bowman's space.

Occasional mesangial hypercellularity appeared in the glomeruli of rats which received 2% lead acetate trihydrate for five months and more. This alteration was increased by increasing the lead doses and period of exposure, and became mild from the eighth month. In addition, mesangial proliferation became more obvious in the kidneys of lead-treated rats in comparison with the control ones, while focal and segmental diffuse eosinophilic glomerulosclerosis was observed in some treated rats after 9 months of lead exposure. Glomerulosclerosis was seen with and adjacent to the area of cortical fibrosis and to the area of interstitial inflammation. Hyaline materials were detected in the mesangium of some lead-treated rats. This change was seen in the glomeruli of the rats which received 2% lead acetate trihydrate for 10 months and more. In addition, the glomerular basement membranes of some glomeruli became thickened and stumpy blocked (Figure 3). This alteration was seen in the kidney of rats which received 2% of lead acetate trihydrate for 7 months and more.

Interstitial Alterations

Changes in the interstitium of the kidney of the lead treated rats were mainly chronic inflammation and fibrosis. Interstitial chronic inflammation was seen at a level of 2% lead acetate trihydrate for 3 months or more. The inflammatory cells seen were mainly plasma cells, and to a lesser extent, lymphocytes. These foci of chronic inflammation were present between tubules or next to glomeruli.

Foci of interstitial fibrosis appeared in the medulla after 8 months of exposure to 1% lead acetate trihydrate while clear fibrosis appeared in the medulla of some rats which received continuous 2% lead acetate for 11 months, where the inter-tubular connective tissue increased in severity and the tubules became widely separated from one another by

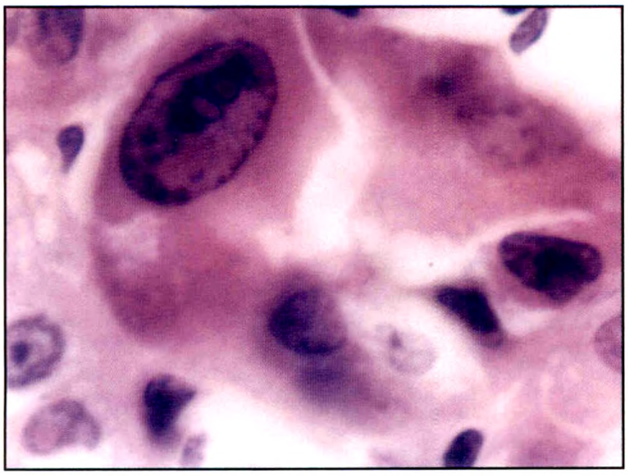

FIGURE 1. Light micrograph sections shows intranuclear inclusion body, 0.5% lead acetate trihydrate for 5 months (H&E, 800x).

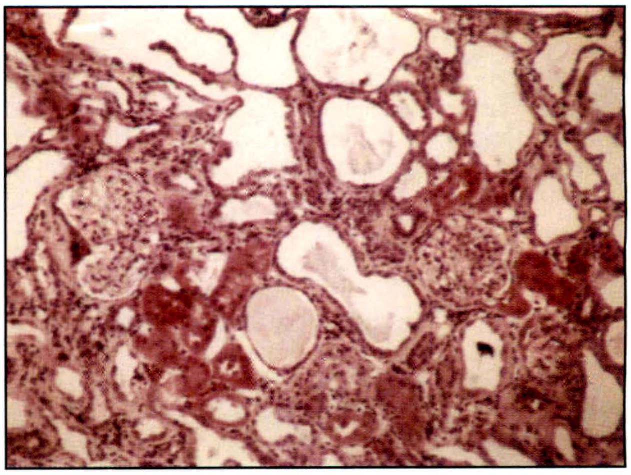

FIGURE 2. Light micrograph sections shows cysticaly dilated proximal tubules with extensive tubulointerstitial injury, 2% lead acetate trihydrate for 10 months (H&E, 250x).

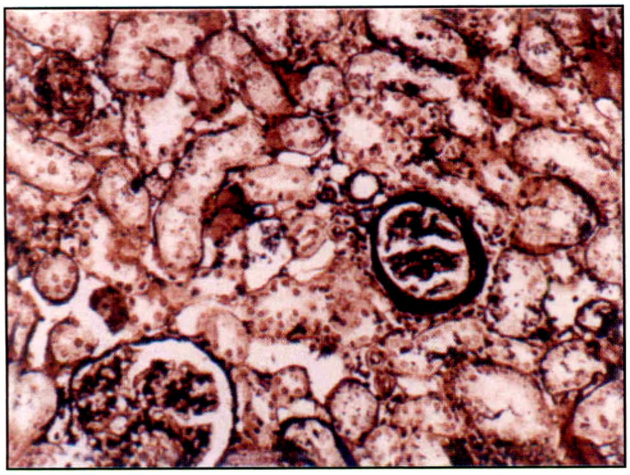

FIGURE 3. Sections shows glomeruloscerosis and thickening of glomerular basement membrane, 2% lead acetate for 8 months (Jones methenamine-silver nitrate method, 250x).

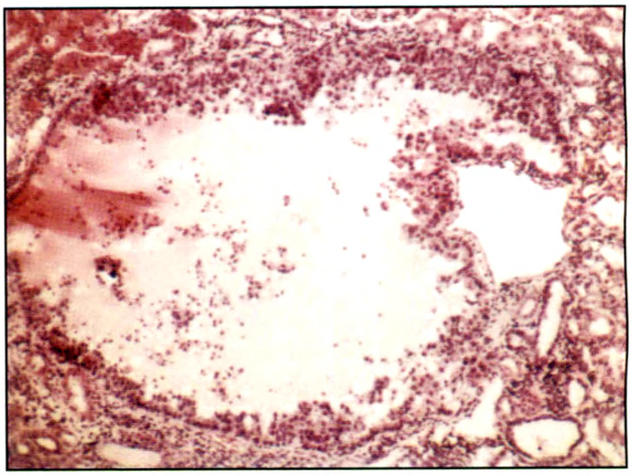

FIGURE 4. Section shows atypical tubular hyperplasia, 2% lead acetate trihydrate for 12 months (H&E, 150x).

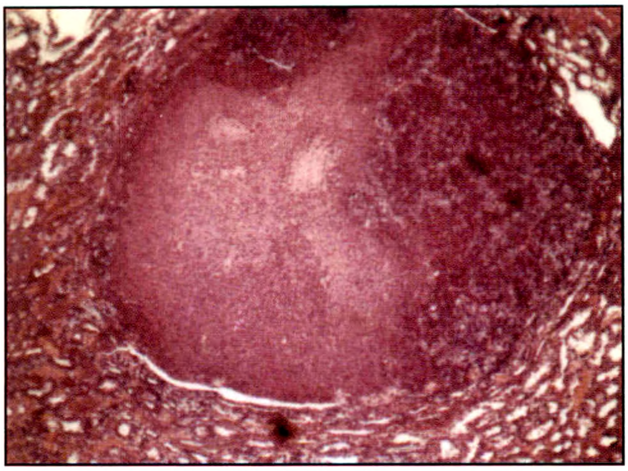

FIGURE 5. Light micrograph sections shows well-differentiated solid tubular adenoma, 2% lead acetate trihydrate for 12 months (H&E, 150x).

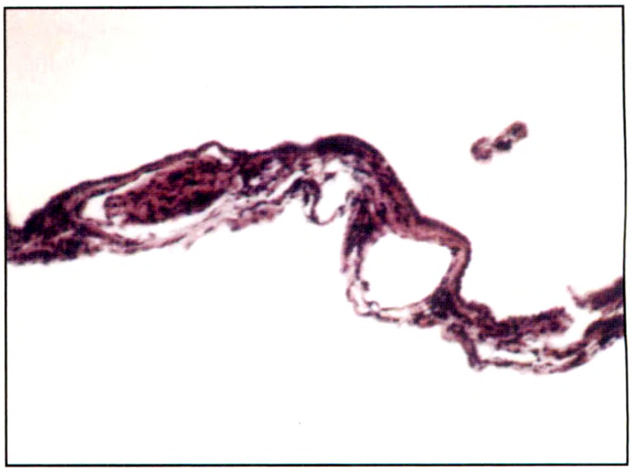

FIGURE 6. Light micrograph sections shows renal cyst wall with sclerotic glomerulus, 2% lead acetate trihydrate for 12 months (H&E, 150x).

endomatous interstitial tissue. The interstitial fibrosis was accompanied with occasional focal patches of chronic inflammatory cells extending from the cortical surface towards the outer medulla. At this stage of histological renal damage, periglomerular fibrosis became prominent together with glomerular sclerosis and tubular basement membrane accentuation.

Thin and thick segments of the loop of Henle showed very little or no alterations due to lead intoxication, while occasional cytomegaly and occasional luminal dense hyaline casts were the only alterations observed in the collecting tubules.

The interstitial matrix of renal papilla appeared normal in all treated rats of all experiment groups. Von Kossa and alizarin red histochemical techniques used in the present investigation could not detect intracytoplasmic calcification in the renal papillae of any of the treated rats. In addition, no thickening, obliteration, hyalinization, adventia scaring or elastic fiber atrophy were observed in the renal blood vessels of any of the experimental animals used in the present investigation.

Renal Tumors

Occasional true tumors in the form of microadenomas were observed in 3 rats of the experimental group which received 2% lead acetate trihydrate for 11 months and more. Some isolated tubules showed few intralaminal papillary formation or hyperplastic lining as an early indication of neoplastic changes. Preneoplastic lesions in the form of atypical tubular hyperplasia and tubular adenomas were detected. The tubular hyperplasia composed of single tubules with *in situ* abnormal changes with several cells lining the tubule without disruption of the basement membrane (Figure 4), while adenomas were mainly in the form of tubular hyperplasia and well-differentiated solid tubular adenoma (Figure 5).

Renal Cyst Dysplasia

Cystic kidneys of some lead-treated rats appeared enlarged as a mass of fibrous tissue and the parenchyma showed varying degrees of atrophy (Figure 6). These cystic fibrotic kidneys showed sclerotic glomeruli and scattered chronic inflammatory cells infiltrates. The tubules were often dilated, and some were filled with pink casts which gave an appearance of thyroidization.

Hemosiderosis

Prussian blue positive granules were observed in the lumen of some renal tubules and the cytoplasm of some interstitial macrophages of rats exposed to 2% lead acetate trihydrate for 7 months and more.

Discussion

The results of the present investigation showed that the subtoxic chronic lead exposure causes slow progressive tubular, glomerular and interstitial damages, together with tubular hyperplasia, microadenomas and renal cysts. Some of these findings are in agreement with some results of previous investigations.[25-29] The varieties in the histological alterations of the renal tissues due to lead intoxication obtained by different investigators could be due to the variations in the level of exposure, duration, route of administration and animal species used in the experiments.

The data of the present work showed that the cortex is more affected than the medulla due to long-term treatment with lead. This could be partly due to the uneven distribution of lead in the tissue of the kidney where about 90% of the total renal blood flow enters the cortex via the blood stream. Accordingly, a relatively high lead might reach the cortex via the blood stream than that would enter the medulla.

Karyomegaly and intranuclear inclusion bodies were the early histological alterations which developed due to long-term intoxication. This confirms that the nucleus is the key factor in most cell disturbances,[30] and undergoes morphological and functional alterations due to lead poisoning. Several investigators have described the development of the intranuclear inclusion bodies due to chronic lead exposure,[16,18] and considered it as an adaptation to the metabolic and functional changes in the organelles of renal cells due to lead intoxication. A histochemical characterization of the intranuclear inclusion bodies showed that these bodies are lead lipoprotein complexes containing sulfyhydryl groups and are basic in nature.[31]

Cellular inclusions, whether cytoplasmic or nuclear, usually serve as a pathological hallmark and results from metabolic disturbances.[32] The development of the intranuclear inclusion bodies due to lead poisoning would seem to be somehow a pathological event resulting from lead exposure more than an adaptation to the effects of intoxication. The development of other pathological events, especially the nuclear pleomorphism such as karyomegaly, karyolysis, etc, supports the suggestion that lead intranuclear inclusion bodies might be an indication of metabolic and structural disturbances as a result of lead detoxification mechanism rather than an adaptation to lead intoxication, and a relationship between the size of inclusions and the degree of cellular alterations seems to exist.

The histochemical characterization of the cytoplasm inclusions induced by lead toxicity as shown in the results of the present study might indicate that these inclusions are composed of oxidative lipids and lipoproteins associated with lead and have lipofuscin nature. This result could indicate that lead poisoning increases lipids oxidation. The results of the present work showed that the cytoplasmic inclusions produced due to lead intoxication were less frequent than the intranuclear inclusions. This might be due to the degradation of the cytoplasmic inclusions by the lysosomal systems.

The findings of the present work showed that the tubular damages were more prominent in the proximal convoluted tubules in comparison to that in the distal ones. This could be due to the fact that the proximal convoluted tubules are the primary sites of reabsorption and active transport leading to higher concentration of lead in the epithelial lining of the proximal tubules. Tubular vacuolization, necrosis and dilation found in the present study due to lead intoxication have been reported by other workers.[20,33,34] These tubular alterations due to lead toxicity might be a result of a hydrologic changes in the renal tissue and suggest that lead intoxication is an injurious stimulus that yields to a partial failure in the ion pump transport of tubules cells which in turn produces tubular swelling and causes necrosis and vacuolization of proximal tubules cells. The presence of proteinaceous droplets and hyaline casts in the lumen of the damaged tubules is an indication of glomerulonephritis and represent partial failure of tubular reabsorption. The kidney is rich in acid glycocidases and proteolytic enzymes located in lysosomes and other subcellular compartments.[35] The glycoprotein content of the hyaline casts produced due to lead intoxication may indicate an action of glycosidases and proteolytic enzymes on the cell component of injured cells.

The main interstitial alterations in the kidney of lead-treated rats were mainly focal and segmental fibrosis with chronic inflammatory infiltration in the interstitium. Similar findings were reported by previous studies.[16,18,36-38]

Some lead-treated rats showed renal cysts after 11 months and more of lead exposure. This alteration is an indication of renal failure and hydronephrosis where these cysts arise as a result of nephrons blockage, with subsequent dilation and parenchymal dilation of the renal tissues. The previous investigations on the histological alterations mentioned very little, if any, of the renal cyst formation due to long-term lead exposure.

The formation of microadenomas in the kidneys of some lead-treated rats is an indication of tumor risk. The mechanism of oncogenic action of lead is only poorly defined. Some workers have reported precancerous and adenomatous lesions in kidneys of rats exposed to lead for 12 months,[39-40] and others have reported renal carcinoma due to lead intoxication in other experimental animals.[16,41] Selevan et al.[42] reported increased mortality from renal cancer in lead smelter workers, although the data from human studies are inadequate for evaluating the potential carcinogenicity of lead.[43] In contrast, renal hyperplasia or neoplasms were not reported by Hirsch[6] or Fowler et al.[12] in rats exposed to lead in the diet and drinking water, respectively. Based primarily on rodent data, carcinogenically effective levels of lead was generally estimated to range from 0.1%-1% lead and require a 12-24 months period of continuous feeding to be active and is rated as a possible human carcinogenesis where continuous chronic lead exposure induces adenomas and adenocarcinoma.[19,40,41]

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A NEONATAL SCREENING IN LEBANON: RESULTS OF FIVE YEARS' EXPERIENCE

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Background: Neonatal screening programs for common disorders like phenylketonuria, congenital hypothyroidism, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are not fully established at the national level in Lebanon. Screening for the above disorders was carried out for newborns delivered at the American University of Beirut Medical Center over a period of five years.

Subjects and Methods: Blood specimens collected 2-3 days after birth were applied to neonatal screening blood collection cards. A total of 9117 newborns were screened using phenylalanine, thyroid-stimulating hormone, and G6PD activity measurements on blood spots.

Results: One case of phenylketonuria and another of hyperphenylalaninemia were detected. We also detected 5 cases of permanent type congenital hypothyroidism, giving an incidence of 5:9117 (1:1823). The age range at initiation of hormonal replacement therapy was 9-46 days. The overall incidence of G6PD was 106:9117 (1:86 or 1.16%), of which 84 had complete deficiency (1:109 or 0.92%), and 22 with intermediate activity.

Conclusion: The incidence of these disorders found in this Lebanese sub-population warrants consideration of a comprehensive nationwide neonatal screening program.

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Key Words: Neonatal screening, phenylketonuria, congenital hypothyroidism, glucose-6-phosphate dehydrogenase deficiency.

The mass population screening for phenylketonuria (PKU), congenital hypothyroidism (CH), and glucose-6-phosphate dehydrogenase (G6PD) deficiency started between the 1960s and 1980s.[1-3] Seventeen percent of pediatric hospital admissions in Lebanon are due to PKU, CH, and G6PD deficiency.[4]

PKU is an inherited disorder of phenylalanine metabolism affecting 1:10,000-1:12,000 newborns.[5] Since the introduction of blood screening for PKU, mental retardation has virtually been eliminated, except for some persistence of learning difficulties.[6] The worldwide incidence of CH varies between 1:3000-1:4000 newborns.[7] Physical diagnosis alone can detect the condition in less than 5% of cases at birth and in about 34% before the age of three months.[8] Without prompt treatment, most affected children gradually develop growth failure, irreversible mental retardation, and a variety of neuropsychological deficits.[8,9] Early identification and therapy before three months of age may completely reverse the outcome.[10] G6PD deficiency is often associated with neonatal jaundice secondary to acute hemolysis on exposure to oxidative stress.[11] The incidence of the disease varies among countries and within regions of the same country, being highest in the Mediterranean region and among Kurdish Jews.[12] The incidence reaches up to 1:4 in boys and 1:8 in girls in the Eastern Province of Saudi Arabia.[13] Comprehensive screening with good health educational programs are important to substantially decreasing the number of cases of favism in high incidence areas. In this study, we report the results of a five-year systematic screening program for PKU, CH, and G6PD deficiency done at the American University of Beirut Medical Center (AUBMC).

Subjects and Methods

Sample Collection

Whole blood was collected in EDTA anticoagulated micro tubes (0.3 mL) 2-3 days after birth. It was then applied to filter paper, left to dry for 3 hours at room temperature, and stored at 4°C in a nylon zip-lock bag. Cord blood was collected and applied similarly. The blood collection cards were stable: 1 week for G6PD, 6 months for phenylalanine, and 4 months for thyroid-stimulating hormone (TSH) analysis. Using the DELFIA puncher (WALLAC Oy, Turku, Finland) a 3 mm disk was used for each assay. Results were identical for all three analytes

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when comparing anticoagulated and directly applied blood (TSH comparison, P=0.31 for paired t-test, and Pearson correlation = 0.98).

Phenylalanine

Phenylalanine was determined by an enzyme assay from ICN Biomedicals (Costa Mesa, CA, USA). The assay has a reportable range of 42.0–1560.0 µmol/L. Precision was less than 13% at levels of 277, 449, and 802 µmol/L. Accuracy was above 85% at targets of 240, 456, and 850 µmol/L. Results above 240 µmol/L were considered abnormal and repeated (false-positive rate = 5.0%). Confirmation using high performance liquid chromatography was done on a second sample for results consistently above 240 µmol/L. Results were reported as negative or positive.

Thyroid-Stimulating Hormone (TSH)

The DELFIA neonatal hTSH kit (WALLAC Oy, Finland) was used to determine TSH with overnight incubation. The assay has a reportable range of 1.0-250.0 mU/L. Precision was 11.3% and 7.7% at mean TSH levels of 13.3 and 51.8 mU/L, respectively. Accuracy was close to 98% at mean TSH levels of 14.5 and 58.0 mU/L. Any result above 20 mU/L was regarded as abnormal, and another serum sample was requested for TSH, T4 or free T4 determination. Patients were not treated if serum TSH was between 20-30 mU/L. When the repeated serum TSH was above 30 mU/L with low T4, the diagnosis of congenital hypothyroidism versus transient hypothyroidism could not be delineated, and replacement therapy using eltroxin was initiated. When permanence of hypothyroidism could not be established in the newborn period using biochemical findings and clinical manifestations,[14] confirmation was planned at the age of 2-3 years after a 4-week withdrawal of eltroxin treatment in some cases. Definitive diagnosis was also aided by imaging studies (ultrasound or scintigraphy) in other cases.[15]

G6PD

A visual, qualitative enzymatic method was used for the analysis of red blood cell G6PD activity (Kornberg, Sigma Diagnostic Procedure No. 400). The final reaction mixture included: two 3 mm punched disks and 0.5 mL of substrate containing 23.7 µmol Tris (hydroxymethyl) aminomethane, 0.625 µmol G6P, 0.025 µmol nicotinamide adenine dinucleotide phosphate, 0.375 µmol magnesium chloride, 25 µg dichlorophenol indophenol, and 12.5 µg phenazine methosulfate at a pH of 8.0. It was then incubated at 37°C in subdued light after layering 0.5 mL of mineral oil. Three levels of controls (deficient, intermediate, and normal) from Sigma were applied to collection cards and included for each run. The reaction was observed at 15-minute intervals and up to one hour for a change in color. For deficient samples, quantitative determination of G6PD activity was recommended for confirmation.

Results

Over the study period, 5128 males and 4841 females were born, of which 733 were preterm. Multiple deliveries included 271 twins, 26 triplets, and 3 quadruplets. Screening for PKU, CH, and G6PD deficiency was carried out on 9117 newborns.

Two female babies had abnormal phenylalanine results. The first had classic PKU with phenylalanine level of more than 1000 µmol/L and a follow-up level of 777 µmol/L after three months. The second baby had hyperphenylalaninemia (HPA) at 3 days of age (phenylalanine = 284 µmol/L), with a positive family history of a 16-year-old brother diagnosed with HPA which was controlled by diet restriction only.

A total of 48 babies had TSH results greater than 20 mU/L (0.5%). The 27 babies with TSH between 20-30 mU/L were normal when the results were repeated and were not treated. Treatment with eltroxin and long-term follow-up was done only for 12 of the 21 babies with TSH above 30 mU/L. Five babies were confirmed to have permanent CH (Table 1), showing typical CH features since birth. Eltroxin doses were increased in all of the CH babies due to low T4 levels upon follow-up. One patient (no. 3) was a premature baby who had many complications that delayed her neonatal screening (Table 1). The other 7 babies with TSH above 30 mU/L were confirmed to have transient type hypothyroidism using, any combination of these criteria: 1) normalization of TSH levels with decreased requirement of eltroxin; 2) normalization of TSH levels after eltroxin withdrawal for a minimum of 30 days at 3 years of age; 3) adequate growth and development; and 4) definitive finding of thyroid tissue by ultrasound.[16] This gives an incidence of 1:1302 for transient hypothyroidism.

A total of 106 patients had abnormal G6PD activity. The overall incidence was 106:9117 (1:86 or 1.16%), of which 84 had complete deficiency (1:109 or 0.92%), and 22 with intermediate activity. The female to male ratio was 1:2.8 in the deficient group. The incidence of complete G6PD deficiency in males was 1.2%. Twenty-nine out of the 106 patients manifested hyperbilirubinemia requiring phototherapy, and 7 underwent exchange transfusion.

Discussion

Hyperphenylalaninemia

To minimize false-negative results in newborns, samples should be collected on day 4 of age or after in order not to miss any case of PKU.[5,17] In our study, patients were screened for PKU before discharge at 2-3 days after birth in 85% of newborns; the literature reports that 93% of all infants are screened before discharge.[18] Although we detected only two cases of increased phenylalanine, one of which was PKU, we still could have missed others. A larger pool needs to be screened to have a statistically significant

TABLE 1. *Thyroid function and findings in treated infants with hypothyroidism.*

		Screening		Repeat				
Sex	Weeks (gestation)	Age (days)	TSH (m/U/L)	Age (d)	Serum TSH* (mU/L)	T4** (nmol/L)	Age at Tx(days)	Thyroid Scan
F	34	3	>250	28	>100	6.7	25	NP
F	39^{+2}	3	>250	12	>100	8.1	9	Scintigram at 3 weeks (Agenesis)
F	28	33	>250	28***	>100	16.8	46	NP
M	40^{+2}	1	159	15	>100	3.1	15	NP
F	33	12	41.7	15	40.0	78.7	15	NP

Tx=treatment; NP=not performed; T4=thyroxine; FT4=free thyroxine; *the normal age range of serum TSH (mU/L): 1-3 weeks <10, 1-12 months 0.3-5.0; **the normal age range of serum T4 (nmol/L): 1-3 week 105.8-214.1, 1-12 months 92.9-201.2.***this specimen was collected at day 28 before the screening specimen.

number reflecting the real incidence of PKU in our population.

Hypothyroidism

Our results show an incidence of 1:1823 for CH, which is more than twice the worldwide incidence of 1:3000 to 1:4000.[7] Three out of the 5 CH babies were preterm, showing a higher incidence in the preterms (1:244). This finding is consistent with reported increased risk of primary hypothyroidism in preterm infants.[19] Gender distribution for CH was higher in females (4:1), however, this ratio might not reflect the true distribution due to the relative small number of babies screened. The female to male ratio for babies with abnormal TSH results of 1.37:1 is not different from the ratio of CH in the Mediterranean region (1.5:1).[20] and 5:3.[21] Differences in the incidence of hypothyroidism are more likely due to iodine deficiency or the screening method used rather than to ethnic affiliation.[7] Iodine deficiency exists in many areas of Lebanon,[22] however, the iodine status of mothers and screened babies was not assessed. Although iodine deficiency causes transient type hypothyroidism, it would be difficult to distinguish it from the permanent type during the screening period, since definitive diagnosis can only be made after the age of 3 years.[23]

Since the time of screening for CH in our program was between 1-33 days, treatment allowed adequate growth and development in all confirmed babies. This was not possible in previously diagnosed cases in Lebanon, where most of the cases were detected after the age of 1 year and none before 3 months.[22] The time of screening premature neonates (28-35 weeks gestational age) ranged between 12-33 days. Selecting the proper time to screen such babies was a dilemma. Studies have shown that the prevalence of severe transient hypothyroxinemia is increased in the early weeks of life.[24-25] Rooman et al. showed that early preterm neonates have free T4 levels on day 14 that are much lower than that generally assumed while TSH remained in the normal range. Therefore, it was proposed to measure free T4 in all preterms with gestational age below 33 weeks during the second week of life.[26]

After reviewing our results for CH, improvements in our program can be achieved through the following considerations: First, the frequency of abnormal TSH results can be reduced by almost half, if age-adjusted reference ranges are used, especially in the first 3 days of life.[27] Second, infants with non-elevated TSH and low thyroxine that might be missed by TSH testing alone can be prevented by clinical suspicion and re-screening using both TSH and T4.[16,28]

G6PD Deficiency

G6PD deficiency is a sex-linked disease. Enzyme activity and mass do change at different stages of the circulating RBCs.[12,29] The G6PD phenotypes reported for the Lebanese population are G6PD B (97.9%) and G6PD B– (2.1%).[30] Genotypic analysis of G6PD-deficient variants showed that most Middle Eastern subjects acquired the *Gd* Mediterranean allele.[30,31] The incidence of 0.92% (1.2% in males) for complete deficiency in our study is lower than the two previously reported incidences where 549 (3.09%)[4] and 282 Lebanese men (2.13%) were screened in Kuwait.[30] The small sample size of these earlier studies and the methods used for screening probably accounted for these higher rates when compared to our study. Our determined incidence for Lebanese males is lower than reported values from other countries in the region like Syria (2.98%), Jordan (3.6%), and Kuwait (5.51%)[30], yet higher than that for Ashkenazi Jews (0.4%).[12] As for sex distribution, the female to male ratio of 1:2.8 is commensurate with that reported in our region: 1:2.1 in Saudi Arabia[13] and 1:2.4 in Greece.[29]

History of the Program: Problems and Solutions

The screening program at AUBMC for CH, PKU, and G6PD deficiency started in May 1996. G6PD was included in the program due to its prevalence in the Middle East. Qualified endocrinologists were also present to educate and follow up these patients.

Blood was first collected directly on filter paper. After a thorough investigation and to eliminate recollections, blood was collected in EDTA tubes and adequately applied onto the cards in the laboratory.

G6PD and TSH were done on cord blood at the beginning, necessitating another collection for phenylalanine testing 48 hours later. This collection was discontinued 2.5 years later and only one collection for all three analytes is now done in the nursery prior to discharge. The incidence of missed cases declined from 15.0% in the first 2.5 years to 1.2% in the fourth year to reach 0.0% in the fifth year. Considering our incidences for CH (1:1823) and G6PD deficiency (1:109) and the overall number of missed cases (852), we can assume that 1 case of CH and not more than 8 cases of G6PD deficiency could have been missed. We also faced some limitations in the follow-up of patients from low-income class due to restricted communication facilities and lack of parental cooperation.

The program we established may be used as a model for a nationwide screening program, mandated and fully supported by the government.[32] Insuring adequate health awareness and education of parents through a nationwide campaign will improve early detection and parents' cooperation. A national registry that provides disease surveillance and monitors the efficiency and effectiveness of neonatal screening is also essential in helping to identify possible etiological risk factors in PKU, CH, and G6PD deficiency.

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FLUORIDE LEVELS IN DRINKING WATER IN THE CENTRAL PROVINCE OF SAUDI ARABIA

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Background: This study was designed to assess the fluoride levels in drinking water in the Central Province of Saudi Arabia.
Materials and Methods: A total of 817 water samples were collected from 260 locations in Central Saudi Arabia. An atomic absorption spectrophotometer [HACH instrument, model DR 3000] was used in the analyses of water samples for fluoride levels.
Results: The results showed that fluoride levels vary between 0.00 and 6.20 ppm. About 75% and 6% of the population in Riyadh and Qassim regions, respectively, were exposed to very low fluoride levels (0.00-0.30 ppm), while less than 3% of the population in both regions were exposed to fluoride levels ranging from 0.61 to 0.80 ppm. A higher percentage of the population in Qassim than Riyadh region were exposed to high fluoride levels (>0.81 ppm); 28.63% than in Riyadh with 9.24%.
Conclusions: The findings of this study can serve as a baseline data for water fluoridation and other dental preventive programs in the area.
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Key Words: Drinking water, fluoride levels, absorption spectrophotometer.

Exposure to fluoride in drinking water has been shown to be beneficial for oral and general health,[1-5] especially in relation to dental caries and osteoporosis. In a study carried out in 21 cities in four states in the US, Dean et al.[1] showed that exposure to water containing about 1 ppm fluoride in drinking water reduced caries experience by 50%. However, fluoride levels higher than 1.5 ppm in temperate countries is known to cause dental fluorosis.[2]

The earliest study of artificial water fluoridation was carried out in Grand Rapids, USA.[3] The reduction in caries, averaged between 40%-65% in permanent teeth. In a review of 55 fluoridation studies in the literature between 1956 and 1979, Murray and Rugg-Gunn[10] concluded that caries reduction in deciduous teeth was 40%-50%. Furthermore O'Mullane et al.[11] reported a 40% difference in caries prevalence in deciduous teeth of Irish children residing in fluoride-deficient and fluoridated communities. A symposium devoted to fluoride—the International Collaborative Research On Fluoride: Research Needs Workshop—was held in May 1999, Maryland, USA.[12]

In Saudi Arabia, drinking water is obtained from several sources including desalinated seawater, as well as ground water from wells.[6] More recently, bottled water has been gaining popularity.[7] Kordy and Fonseka[8] have reported that public water supply in Riyadh city was within the optimal range for dental health, while Mohamed and Fattah reported flouride levels of 0.26-0.43 ppm in the drinking water of Riyadh.[9] However, there is little detailed information on the geographical distribution of fluoride levels in drinking water in various parts of the Kingdom. The purpose of this study was, therefore, to determine the fluoride levels in the drinking water in the Central Province of Saudi Arabia with a view to producing a fluoride map of the area.

Materials and Methods

The water sampling strategy in this study was designed to cover the whole Central Province of Saudi Arabia, especially the populated regions. In this attempt, it was found that the presence of teaching schools (primary, intermediate and secondary) is a good indicator of heavily populated areas. Based on this premise, every city, town, and village with a school was regarded as a potential site for obtaining water samples.

The surface area of the Central Province (Riyadh and Qassim) is 4,780,780 km^2, with a population of about 4 million. Maps were obtained from several sources showing

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TABLE 1. *Sources of drinking water in Riyadh region and the level of fluoride concentration.*

	Samples	Fluoride concentration (ppm)		
Source	No.(%)	Minimum	Maximum	Mean
Disalinated water	30 (5.5%)	0.13	0.51	0.24
Ground water treated by government plant	397 (73.1%)	0	5.30	0.89
Ground water treated by private plant	103 (19%)	0.02	3.20	0.64
Untreated ground water	13 (2.4%)	0.30	3.30	0.72
Total	543 (100%)			

TABLE 2. *Sources of drinking water of Qassim region and the level of fluoride concentration.*

	Samples	Fluoride concentration (ppm)		
Source	No.(%)	Minimum	Maximum	Mean
Ground water treated by government plant	195 (71.2%)	0.02	4.60	0.95
Ground water treated by private plant	68 (24.8%)	0.04	6.20	0.98
Untreated ground water	11 (4%)	0.06	2.30	0.68
Total	274 (100%)			

TABLE 3. *Water collection points.*

	Riyadh	Qassim	Total
Source	No. of samples (%)	No. of samples (%)	No. of samples (%)
Primary school	253 (46.6%)	129 (47.1%)	382 (46.8%)
Intermediate school	88 (16.2%)	66 (24.1%)	154 (18.9%)
Secondary school	50 (9.2%)	52 (19%)	102 (12.5%)
Private plant	96 (17.7%)	16 (5.8%)	112 (13.7%)
Government supply	42 (7.7%)	11 (4%)	53 (6.4%)
Well water	14 (2.6%)	–	–
Total	543 (100%)	274 (100%)	817 (100%)

the distribution of cities and villages that would be the potential targets for our investigation. The Ministry of Education and the Presidency of Girls Education were contacted in order to determine the distribution of schools in the Central Province of Saudi Arabia.

Each of the water samples was collected, using 500 mL polythene bottles. The collection of the samples was done during the daytime. The tap water was allowed to run for a few minutes before obtaining the sample. The bottles were first washed three times with the water prior to the collection of about 300 mL of the sample. The water sample was analyzed for fluoride within one week of sample collection, using the atomic absorption spectrophotometer (HACH instrument, model DR 3000). The standardization and validation of the analysis of water samples were done according to the manufacturer's instructions. A standardized solution with a known fluoride concentration (Hach Company, USA) was used for the calibration of the instrument before each set of tests. The statistical significance of the difference between fluoride exposure in Riyadh and Qassim regions was determined, using the chi square test.

Results

This study identified two main sources of drinking water in the Central Province of Saudi Arabia: ground water and desalinated seawater. About 4% of the sample came from desalinated water, while the remainder was from ground water, some of which was treated by the government or private plants. The sources of drinking water and fluoride concentrations are shown in Tables 1 and 2.

A total of 817 water samples were collected from 260 locations, 179 of which were in the Riyadh region and the remaining 81 from the Qassim region. Most of the water samples were collected from water sources located in school premises.

Fluoride levels were found to vary between 0.00 and 6.20 ppm. The highest level of 6.20 ppm was recorded at Al-Madnab (Qassim region), while there was virtually no fluoride in the drinking water in Darul Baida (Riyadh region). Generally, fluoride levels were higher in Qassim than in Riyadh region (Table 3 and Figures 1 and 2). The study also showed that the population of Riyadh and Qassim regions exposed to varying fluoride levels in their drinking water (Figure 3). About 75.4% and 6.3% of the population in Riyadh and Qassim regions, respectively, are exposed to very low fluoride levels (0.00-0.30 ppm), while less than 3% of the population in both regions are exposed to the fluoride levels ranging from 0.61-0.80 ppm. A higher percentage of the population in Qassim than Riyadh region is exposed to high fluoride levels (≥0.81 ppm): 28.63% in Qassim as against 9.24% in Riyadh region. Chi-square test showed this difference to be statistically significant ($P<0.05$).

Discussion

Schools were used in this study as an indicator of population distribution. It is government policy to provide free schooling facilities to the entire population in Saudi Arabia. Therefore, the presence of schools would indicate high population concentrations, in contrast to the desert areas that are sparsely populated.

The fluoride levels of 0.0-6.20 ppm in drinking water in the present study is higher than the fluoride concentrations of up to 2.5 ppm reported for the Makka area[13] and the Hail region[14] of Saudi Arabia where dental fluorosis is endemic. It is therefore to be expected that dental fluorosis would be prevalent in many areas of the Riyadh and Qassim regions. Investigation into the relationship between fluoride levels in drinking water and severity of dental fluorosis in the Central Province of the Kingdom is, therefore, of interest.

Our study shows that over 75% of the population in Riyadh region are exposed to very low fluoride levels of 0.00-0.30 ppm. It has been suggested that the optimal fluoride level in drinking water in communities where ambient temperature is above 27°C should be

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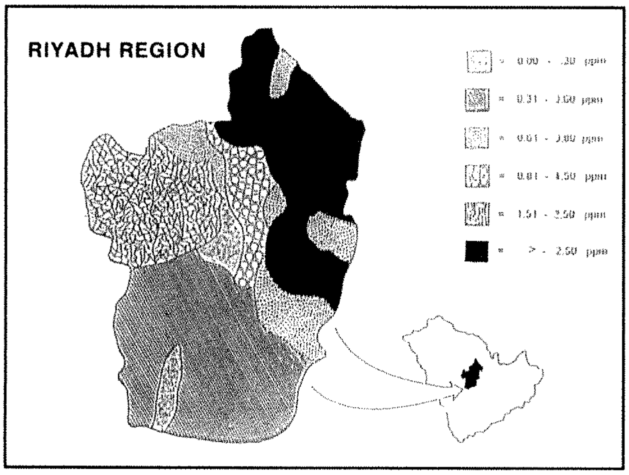

FIGURE 1. Fluoride concentration zones in Riyadh region.

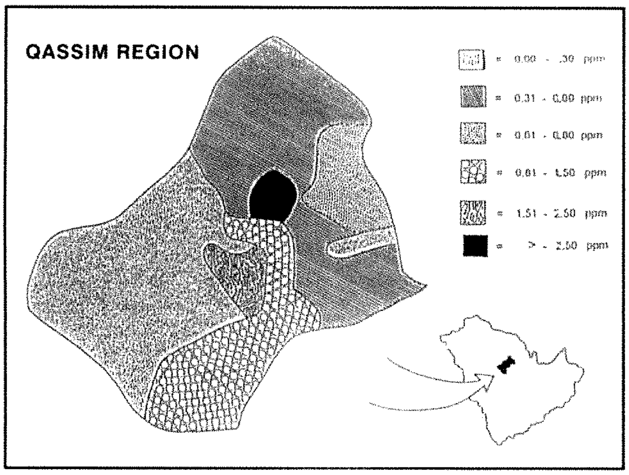

FIGURE 2. Fluoride concentration zones in Qassim region.

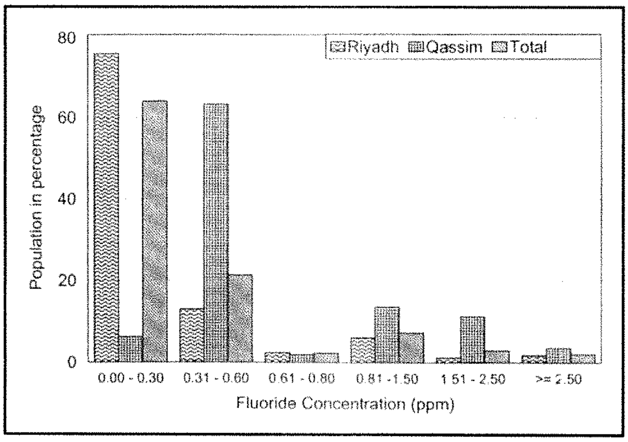

FIGURE 3. Population distribution among the different fluoride zones.

approximately 0.6-0.8 ppm,[15] while Brouwer et al.[16] recommended an optimal fluoride level of 0.6 ppm for Senegal, a tropical West African country. These recommendations appear to take no cognizance of other sources of fluoride intake such as diet,[17] beverages,[18] infant formula and fluoride tooth pastes.[19] In a recent study in Iran, Zohouri and Rugg-Gunn[20] suggested that the 3-4-year-old-children exposed to 0.30-0.39 ppm fluoride in drinking water ingested 0.03 mg F/kg body weight from their diet per day. In addition, these children ingested 0.021 mg F/kg body weight per day from fluoride toothpaste, if they brushed their teeth thrice a day. Thus, the fluoride intake from diet and tooth paste ingestion could reach the optimum value of 0.05-0.07 mg F/kg body weight per day recommended by Ophaug et al.[21] and suggested to be the upper limit of daily fluoride intake by Burt.[22] This further underscores the need for comprehensive studies of fluoride exposure in a community before recommending the use of fluoride supplement or determining the appropriate fluoride level in drinking water for a community.

In the present study, about 12.5% of the population in the Central Province of Saudi Arabia were exposed to fluoride levels above 0.81 ppm. This is excessive for a community in the tropical belt. In 1957, Galagan and Vermillion[23] observed increased water consumption with increase in ambient temperature among California children, implying higher fluoride intake from drinking water as ambient temperature increases. However, in 2001, Sohn et al.[24] found no correlation between daily water intake and ambient temperature among US children. This may be attributed to changing lifestyles as people now spend more time in air-conditioned environment than they did in 1957.

Drinking water in these communities should be defluoridated or else the communities provided with alternative sources of drinking water with low fluoride concentrations. In determining the appropriate fluoride concentration, a balance has to be struck between the cariostatic effect of the fluoride and its potential to cause dental fluorosis. The findings of this study provide an essential baseline data for future planning of dental preventive programs in the Central Province of Saudi Arabia, especially with regards to water fluoridation.

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INCREASED FREQUENCY OF ANGIOTENSIN-CONVERTING ENZYME DD GENOTYPE IN SAUDI OVERWEIGHT AND OBESE PATIENTS

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Background: Several studies have been carried out to investigate the insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme (ACE) in obese and normal weight individuals, often with contradictory results in different populations. In some studies, the DD genotype occurs at a high frequency in obesity, while in others no association has been demonstrated. Since obesity and overweight are of frequent occurrence in the Saudi population, we initiated this study to investigate the I/D polymorphism of ACE in obese, overweight and normal weight Saudis.

Patients and Methods: The study group included 457 Saudi males and females. The height and weight were measured and body mass index (BMI) was calculated. Based on the BMI value, the total study population was classified as normal, overweight and obese. A total of 117 obese (BMI>30 (kg/m^2)), 185 overweight (BMI=25-29.9 (kg/m^2)) and 155 normal weight individuals (BMI<(kg/m^2)) were enrolled. Polymerase chain reaction (PCR) and agarose gel electrophoresis were used to study the ACE polymorphism. For the deletion (D) form, a 190 bp and for the insertion (I) form, 490 bp DNA fragment were obtained on 2% agarose gel electrophoresis.

Results: The frequency of DD genotype was 76.9% in the obese, and 73.5% in the overweight individuals, compared to 19.66% and 24.86% of the ID genotype in the obese and overweight, respectively. Among the normal weight individuals, the frequency was significantly lower for DD and higher for the ID genotype, i.e., 58.7% for DD and 40% for ID. The allele frequencies in the obese were 0.867 and 0.133 for the D and I alleles, respectively. While in the overweight, the frequencies were 0.859 and 0.141 for these alleles, respectively, compared to 0.787 and 0.213 in the normal weight individuals.

Conclusions: The DD genotype and D allele occur at a high frequency in Saudi overweight and obese individuals, and may have some role in fat accumulation by affecting metabolic pathways of fat, thus leading to the development of overweight and obesity.

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Keywords: Angiotensin-converting enzyme (ACE), obesity, overweight.

Angiotensin-converting enzyme (ACE; Kininase II; EC 3.4.15.1) is a dipeptidyl exopeptidase that cleave carboxyl terminal dipeptide of angiotensin I (A-1) to form the octapeptide angiotensin II (A-II) and inactivates the vasodilator bradykinin.[1] Recently, the genes of components of the rennin-angiotensin system, namely angiotensinogen, ACE and angiotensin II receptors, have been described in the adipose tissues and the gene expression of angiotensinogen has been studied in adipose tissues of obese patients.[2-4] The human ACE gene is located in chromosome 17q23 and has 26 exons and exhibits polymorphism caused by either an insertion (I) or deletion (D) of a 287 base pair (bp) alu-type sequence within intron 16, thus resulting in three genotypes: DD, ID and II.[2] Circulating ACE levels show extensive inter-individual variability, and are highly genetically determined.[5] Serum levels vary in the different genotypes, where highest levels are reported in the DD and lowest levels in the II genotypes and the D allele of this polymorphism has been associated with elevated plasma ACE levels and ACE activity in a codominant pattern.[2,6,7] In addition, the activity of the renin-angiotensin system appears to be regulated by food intake, suggesting that it may be involved in development of obesity and obesity related hypertension.[4]

The genotype of ACE DD is shown to be linked to different disorders, including obesity, hypertension, diabetes mellitus and renal disease.[8-16] In addition, it has also been implicated in the development of complications such as hypertension in obese individuals.[17] However, there are several contradictory reports in the literature and ethnic variations are frequent in ACE genotype and phenotype frequencies in healthy and diseased individuals. In this study we investigated the ACE gene polymorphism in

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TABLE 1. *Demographic data of the Saudis included in this study.*

	Normal weight (155)		Overweight (185)		Obese (117)	
	M	F	M	F	M	F
Age (years)	31.4±6.4	32.2±6.6	30.6±17.6	35.4±19.02	33.8±16.5	34±13.9
BMI (kg/m^2)	21.3±3*	20.4±3.2*	27.8±3.2*	27.4±1*	36.2±10.1*	34.4±3.5*
BP (mmHg)						
Systolic	116.4±9.5	115.9±16.8	120±20.1	121±20.6	120±11.5	120±10
Diastolic	76.2±8.5	75.1±8.4	80±9	81±10.7	79±8	80±10.4
Height (m)	1.65±0.07	1.56±0.07	1.66±0.07	1.52±0.05	1.62±0.05	1.54±0.06
Weight (kg)	58.6±9	49.9±7.1	75.3±7.7	64.2±7.5	92.5±12	81.9±10.9

*Difference in the results of normal weight, overweight and obese was statistically significant.

TABLE 2. *Frequency of I/D genotypes and alleles in Saudi overweight, obese and normal weight individuals.*

	Genotype frequency			Allele frequency	
Saudi population	DD No (%)	ID No (%)	II No (%)	D	I
Normal	91 (58.7)*	62 (40)*	2 (1.29)	0.787*	0.213
Overweight	136 (73.5)	46 (24.86)*	3 (1.62)	0.859*	0.141
Obese	90 (76.9)	23 (19.66)*	4 (3.42)	0.867*	0.133

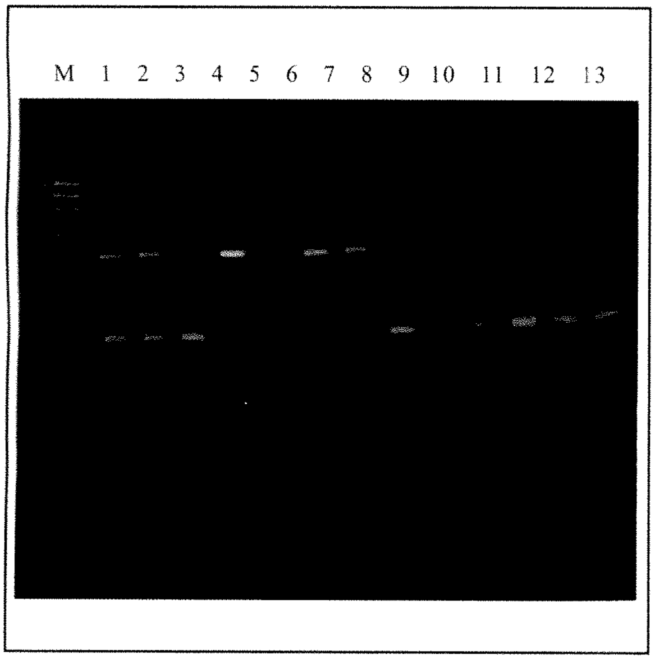

FIGURE 1. Fragments obtained on electrophoresis of the PCR product of amplified Exon 16 of ACE gene in 2% agarose gel (490 bp I allele and 190 bp D allele).

overweight and obese Saudis, and discuss the possible mechanism of its involvement in weight regulation.

Patients and Methods

This study was a part of a major project entitled "Application of Recombinant DNA Technology in Medicine – On the look for Genetic Markers for non-communicable Disorders", approved by the Ethical Committee and Project Review Board at the Research Center for College of Medicine, King Saud University, Riyadh. The study group included 457 Saudis (male 199, female 258) visiting King Khalid University Hospital as blood donors or outpatients for minor illnesses. Informed consent was taken and the individuals were enrolled in the study. Each individual was given a study number and strict patient confidentiality was observed by referring to each patient using the patient number only. Essential details (gender, age, marital status) were recorded. Height was measured using a measuring tape with the individuals standing straight next to the wall, with the heels, buttocks, and shoulders touching the wall. Weight was recorded using a normal weighing scale with the individuals wearing light cloths and no shoes, and the mean of two readings was recorded. The weighing scale was regularly calibrated.

Blood was drawn by venepuncture in EDTA tubes and was used for extraction of DNA by the method of Kunkel et al.[18] The amplification of DNA surrounding the polymorphic site in exon 16 was carried out using published procedure with slight modifications.[2] The amplification mixture (50 μl) contained: 10mM Tris-HC1 buffer pH 8.8; 50 mMKC1, 1.5 mM MgC12, 0.1% Triton X-100; 200 μM each of the four dNTPs, 1 μm each of the two primers (5' CTG GAG ACC ACT CCC ATC CTT TCT 3' and 5' GAT CTG CGG ACT CAC ATT CGT CAG AT 3') 5% dimethylsulfoxide, 80 μg DNA and 2 U of Taq DNA polymerase. The mixture was subjected to denaturation of 3 min at 96°C and amplification was carried out in 30 cycles of: denaturation at 94°C for 1 min, annealing at 65°C for 1 min and extension at 72°C for 2 min followed by final extension at 72°C for 5 min. The PCR product was subjected to electrophoresis in 2% agarose gel and visualized by ethidium bromide.

Data was entered on personal computers and analyzed using SPSS for windows. Chi square (χ^2) analysis were used to compare the frequency of ACE alleles in any two groups. $P<0.05$ was considered statistically significant.

Results

There were 199 adult males and 258 adult females with ages ranging from 18 to 70 years. Quetelet index (body mass index; BMI) was calculated using the formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2\,(\text{m}^2)}$$

On the basis of BMI values, the patients were grouped as normal weight (<25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). The demographic details of the normal, overweight and obese individuals studied are listed in Table 1. Angiotensin-converting enzyme genotypes identified were: II, ID, and DD as shown in Figure 1. The prevalence of each genotype was calculated separately in the normal weight, overweight and obese Saudis (Table 2). The prevalence of the DD genotype was significantly higher in the overweight and obese individuals compared to those with normal weight. No significant gender differences were seen in the results of ACE genotypes.

The allele frequencies of I and D alleles were calculated and are presented in Table 2. The frequency of D allele was significantly higher in the overweight and obese individuals compared to the normal weight group.

Discussion

Circulating levels of ACE exhibit extensive inter-individual variability and are highly genetically determined.[5,6] Several studies have confirmed in different ethnic groups that I/D polymorphism of the ACE gene is a major determinant of the circulating levels of ACE in blood plasma of humans[2,6] and accounts for as much as half of the variability of circulating ACE levels among individuals.[2,19] Other factors also influence the ACE level and these include exercise, diet and body weight.[4,20,21] Elevated ACE levels have been implicated in the pathogenesis of several disorders,[7,8,19-23] though there are some contradictory reports.[7] In addition, the renin-angiotensin system is known to play an important role in metabolism and influence insulin action, thus affecting different metabolic pathways.[4,20,21] It has been implicated in the pathogenesis of metabolic alterations and hypertension associated with obesity.[17] Positive and significant correlation has been reported between the expression of angiotensinogen gene in visceral adipose tissue and BMI, and it has been suggested that angiotensinogen may be a determinant of fat distribution and may be involved in the plurimetabolic syndrome of central obesity.[3] Several studies have shown that obesity is associated with tissue-specific activation of renal angiotensin-converting enzyme, which is independent of its mRNA expression and enhanced vascular contractivity to angiotensin II.[23] In addition, activity of renin-angiotensin system appears to be regulated by food intake.[4] Elevated levels of ACE and angiotensinogen have been reported in obese individuals,[21] and it has been suggested that angiotensinogen-derived peptides, produced in adipose tissues, may affect adipogenesis and play a role in the pathogenesis of obesity.[24] Angiotensin converting enzyme is reported to be involved in producing insulin resistance in overweight individuals.[22] These mechanisms are highly significant in the development of hypertension, diabetes mellitus and other complications in obese individuals.[17]

This study shows close association between the DD genotype and D allele and overweight and obesity in Saudi population. Since D allele results in elevation in ACE activity,[2,6] this may be one of the mechanisms leading to altered ACE levels in overweight and obese patients, leading to insulin resistance, adipogenesis and hence excessive weight gain. This in turn may also be the factor involved in the development of hypertension and diabetes mellitus in overweight and obese individuals.[20-24] Insulin resistance is an important finding in patients suffering from non-insulin dependent diabetes mellitus (type II DM), particularly the obese ones. In some individuals, reduction of body weight decreases the hyperglycemia possibly by decreasing insulin resistance, however, in others there is no improvement in the diabetic state even after weight reduction. It is possible that these individuals have elevated ACE due to the presence of D alleles. Due to the role of angiotensin II in the regulation of blood pressure and a plausible effect on adipogenesis and adipocyte metabolism,[3,4] we hypothesize a possible association between ACE genotypes and development of overweight and obesity. The possible mechanism leading to obesity and its complications such as hypertension need to be elucidated, and further studies are required to confirm the mechanisms involved in the pathogenesis of overweight and obesity.

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EFFECTS OF HUMAN MILK FORTIFICATION ON MORBIDITY FACTORS IN VERY LOW BIRTH WEIGHT INFANTS

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Background: The use of human milk as a sole source of nutrients for preterm infants has been the subject of debate in recent years. We studied the morbidity factors associated with hospitalization of very low birth weight (VLBW) infants fed human milk with and without fortification.

Patients and Methods: One hundred VLBW infants were randomly assigned to two groups with stratification for gestation and weight. The control group ($n=50$; mean birth weight 1239±186 g and mean gestation 29.3±2.1 wks) was fed human milk only, and in the fortifier group ($n=50$; mean birth weight 1245±191 g and mean gestation 29.5±2.1 wks), human milk was enriched with a fortifier after the babies reached a volume of 140 mL/kg/day by the enteral route. Weight was measured twice weekly, biochemical indices of nutritional and bone status and serum electrolytes were obtained weekly, and clinical evidence for sepsis, necrotizing enterocolitis and feeding intolerance was assessed regularly until infants were discharged.

Result: Hospital stay was less than 45 days in the majority (94%) of the babies in the fortifier group, whereas the majority (66%) of the babies in the control group stayed for more than 45 days ($P<0.01$). Low serum phosphorus and raised alkaline phosphatase levels were seen more frequently in the control group without fortification ($P<0.01$), as well as hyponatremia ($P<0.01$), late metabolic acidosis of prematurity ($P<0.01$) and culture-proven sepsis ($P<0.05$). There was no significant difference in the occurrence of necrotizing enterocolitis between the two groups ($P>0.05$).

Conclusion: Human milk fortification has beneficial effects on the growth of VLBW infants and decreases hospital stay and morbidity associated with prematurity and very low birth weight, with economic and psychological benefits for the parents.

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Key Words: Very low birth weight (VLBW) infant, human milk, fortification, morbidity.

Human milk provides adequate nutrition to facilitate optimal growth in term infants, and has potential beneficial effects on immunity and infant-mother bonding. Preterm infants are born with low skeletal stores of calcium and phosphates, and require large amounts of these minerals in order to attain adequate postnatal skeletal growth. The importance of meeting the increased nutritional needs of preterm infants, compared with those of term infants, has been emphasized by many previous studies.[1-4] The aim of this study was to analyze the rate of growth in a large sample of preterm very low birth weight (VLBW) babies fed exclusively on breast milk with or without fortifiers, and to compare the morbidities, including duration of hospitalization, in the two groups.

Patients and Methods

A total of 100 VLBW infants who were appropriate for gestational age and admitted to the Special Care Baby Unit of Khoula Hospital, Muscat, between January 1997 and October 1999, were studied. Since the introduction of the Baby Friendly Hospital Initiative (BFHI) program in the country in 1992, parents have been routinely encouraged to feed all premature babies on breast milk alone. In this double-blind study, infants in one group (control group, $n=50$) received human milk only, while the other group (fortifier group, $n=50$) received fortified human milk. Group allocation was done on the criteria that the groups matched in number, gestational age and birth weight as far as possible. The infants were free of any congenital anomalies. Infants who needed prolonged ventilation were not included in the study.

All infants were fed their own mother's milk, and in case of insufficient breast milk, formula feeds were used to meet the total energy requirements on that particular day. Babies who needed more than 15% of energy from formula feeds for more than two days were not included in this

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TABLE 1. *Nutritional comparison per 100 mL of preterm mother's milk assessed at two weeks postpartum and human milk fortified with 4 g of human milk fortifier.*

Nutrient	Preterm milk	Fortified human milk
Calories (Kcal)	67	81
Protein (g)	1.4	2.4
Fats (g)	3.9	4.06
Carbohydrates (g)	6.6	9.0
Vitamins		
Vitamin A (IU)	389	1289
Vitamin D (IU)	2.0	302
Vitamin E (IU)	1	5.6
Vitamin K (µg)	0.21	11.2
Vitamin B_1-thiamine (µg)	21	247
B_2-riboflavin (µg)	48	298
B_6-pyridoxine (µg)	15	265
B_{12} cyanocobalamin (µg)	0.05	0.35
Niacin (µg)	150	3650
Folic acid (µg)	3.3	33.3
Panthothenic acid (µg)	180	1080
Biotin (µg)	0.6	2.1
Vitamin C (mg)	11	51
Minerals		
Calcium (mg)	25	115
Phosphorus (mg)	13	58
Iron (mg)	0.12	–
Zinc (mg)	0.34	0.60
Magnesium (mg)	3.2	6.2
Sodium (mg)	25	43
Potassium (mg)	57	84
Chloride (mg)	55	72

Milk nutrient composition values from Wyeth-Ayerst International 1999; milk composition literature was used from studies that reported data on milk samples collected from mothers who delivered prematurely.

TABLE 2. *Data of infants fed human milk with fortifier (fortifier group) or without fortifier (control group).*

	Fortifier group (n=50)	Control group (n=50)
Gestational age (wk)		
26-27	8	10
28-30	30	27
31-34	12	13
Mean gestational age±SD (wks)	29.5±2.1	29.3±2.1
Birth weight (g)		
600-1000	4	5
1001-1250	20	19
1251-1500	26	26
Mean birth weight±SD (g)	1245±191	1239±186

study. Milk was expressed by the mothers using Medela breast pump (Medela AG, Medical Technology, Switzerland). Infants were started on feeds as soon as clinical conditions permitted. When the infants tolerated a volume of >140 mL/kg/day by the enteral route, the milk in the fortifier group was enriched with a multinutrient fortifier in the form of a powder in packets, manufactured by a leading multinational drug company. Fortification was started with 1 g of fortifier added to 100 mL of milk on day 1, and gradually increased to 4 g of fortifier added to 100 mL on day 3 or 4 to improve tolerance of fortified milk. Feedings were initially given by continuous, and later by intermittent gavage feeding, and finally the infants were cup and breast fed before discharge. Maximum enteral milk intake was kept at 180 mL of milk/kg/day until the infants were breast-fed. The nutrient content of 100 mL of fortified human milk (with 4 g of fortifier) and mother's milk at two weeks postpartum is shown in Table 1.

Weight was measured twice weekly throughout the study period. Data regarding gestation, birth weight, duration of hospital stay and average daily weight gain were analyzed. Biochemical indices of nutritional and bone mineral status were obtained on the first day of study and weekly thereafter until the infants were discharged from hospital. These indices included serum calcium, phosphorus and alkaline phosphatase levels. Serum electrolytes were also checked weekly after infants were on full enteral feeds. Clinical evidence for sepsis, feeding intolerance and necrotizing enterocolitis was monitored and assessed regularly. The data were analyzed and statistical significance of the observed data was derived using the chi-squared method.

Results

Demographic data shows that the gestational age at birth ranged from 26 to 34 weeks while the birth weight ranged between 600 and 1500 g in both study groups, and that there were no significant weight and gestational age differences in the two groups (Table 2). Overall, insufficient breast milk was not a problem in this study, but 6 infants (3 in the control group and 3 in the fortifier group) received supplemental formula milk over a total period of 7 study days (4 days in the control group and 3 days in the fortifier group) to meet the total energy requirements. The total energy intake from formula over these days was less than 15% on each day. This had no statistical significance on the study objectives both in terms of the number of the patients who received formula supplements in each of the two groups ($P>0.05$), or on the total caloric intake from human milk during the entire period of hospitalization.

Weight gained in grams per day is shown in Table 3. The rate of gain was less than 20 g/day in 43 infants (90%) in the control group and more than 20 g/day in 41 (90%) infants in the fortifier group ($P<0.01$). Duration of hospital stay (from admission date until a weight of 2000 g was achieved) shows that all the infants in the fortifier group were discharged within 60 days, as compared to only 34 (60%) infants in the control group ($P<0.05$) (Table 3).

Serum biochemical values are shown in Table 4. Low serum phosphorus (<1.55 mmol/L) and raised alkaline phosphatase levels (>450 mmol/L) were seen in a significantly higher proportion of infants in the control group as compared to the fortifier group ($P<0.01$). Hyponatremia (<130 mmol/L) and late metabolic acidosis of prematurity were also more evident in the control group ($P<0.01$). Similarly, culture-proven sepsis was seen in 3 (6%) infants in the fortifier group, compared to 7 (14%) in the control group ($P<0.05$). A look at the incidence of

TABLE 3. *Weight gain and hospital stay in the two groups.*

Weight gain (g/day)	Fortifier group (n=50)	Control group (n=50)
<20	9	43*
>20	41	7
Hospital stay (days)		
<30	25 (50%)	1 (2%)
31-45	22 (44%)	16 (32%)
46-60	3 (6%)	17 (34%)
>60	–	16 (32%)

*χ^2=46.29, $P<0.01$.

TABLE 4. *Comparison of morbidity factors in the two groups.*

	Fortifier group (n=50)	Control group (n=50)	χ^2	*P*-value
Low phosphorus	0	16	19.04	<0.01
Raised alkaline phosphatase	5	30	27.44	<0.01
Hyponatremia	6	16	5.82	<0.05
Late metabolic acidosis	0	3	3.08	<0.05
Necrotizing enterocolitis	3	5	0.54	>0.05
Culture-proven sepsis	3	7	1.76	<0.05

Normal values: phosphorus 1.55-2.65 mmol/L; alkaline phosphatase 145-420 IU/L; sodium 134-146 mmol/L.

necrotizing enterocolitis (NEC) shows that there was no significant difference between the two groups in the number of infants (6% vs. 8%) who had this condition during hospitalization ($P>0.05$).

Discussion

Human milk feeding has potentially significant immunologic, nutritional and psychological advantages for the small preterm infant, and there is increasing scientific evidence supporting its value in neonatal care.[5-7] However, the low phosphorus content of human milk may be inadequate for bone mineralization during and after hospitalization,[1] and previous studies have shown improved bone mineralization and growth in premature infants fed fortified mother's milk[3,8] and higher prevalence of osteopenia and rickets in the VLBW infants without mineral supplementation.[4,9] Estimates of calcium and phosphorus needs for infants <1800 g and gestational age of 26-32 weeks are 140-180 mg calcium and 70-90 mg phosphorus/kg body weight/day.[10]

Many studies in the past have focused on various aspects of fortifier-enriched milk for preterm infants.[11-13] The last reported study by Schanler et al.[12] focused on the effects on growth, feed intolerance and health of participating infants who were fed fortified human milk, in comparison with those who were fed exclusively with preterm formula.

Our case-control study focuses mainly on the subject of nutritional morbidity factors in preterm babies. Though bone density could not be measured in this study, the biochemical indices of osteopenia of prematurity clearly show that neonatal well-being during the lengthy hospitalization of VLBW babies can be further improved by the addition of human milk fortifier to breast milk. There is a significant reduction in the duration of hospitalization because of faster growth rate in babies receiving fortification, with economic and psychological benefits for the parents. The shorter duration of hospitalization may decrease exposure of these babies to nosocomial sepsis and thus contribute to the overall reduction of sepsis and the associated morbidity in VLBW babies. Similar observations have been made by Reiss et al.,[13] who found enhanced growth of preterm babies with human milk fortification, and also by Schanler et al.,[12] who noticed that infants fed fortified human milk were discharged earlier and had less incidence of late-onset sepsis and NEC. The other study by Lucas et al.[11] reported higher plasma calcium, more clinical infections and non-significant increased incidence of NEC in the fortifier group. The problem with the study by Lucas et al. has been that the breast milk intake comprised only 47.6% of total enteral intake, and more than 50% of the enteral intake was supplemented by a preterm formula. Therefore, this mixed feeding pattern cannot be relied on to draw conclusions on the complications of fortification of human milk.

We noted that in addition to hypophosphatemia, hyponatremia is also frequently seen in VLBW babies, especially during the initial stabilization and early recovery periods of hospitalization. Our study demonstrated that the frequency of hyponatremia can be reduced by the additional amounts of sodium present in the fortifier, and may alleviate the need for sodium supplementation in recovering LBW babies with hyponatremia. In spite of the marginally higher content of sodium in the milk of babies receiving human milk fortifier, there was no significant difference in the frequency of feed intolerance and NEC in the two groups. This may also be related to the fact that human milk-fed babies have a very low incidence of NEC, as compared to babies on artificial feeds,[14] and fortified human milk, though marginally hyperosmolar than human milk alone,[15] does not predispose to the development of NEC and may be better than hypertonic saline added to the feeds in situations of hyponatremia during recovery periods of these LBW infants.

All these facts further point to the need for initiating fortification of human milk feeds in VLBW babies as soon as these infants tolerate enteral feeds. Though the current practice in most places is to initiate fortification at an enteral volume of 140 mL/kg/day, some recent studies have encouraged the use of fortification beginning at an enteral volume of 100 mL/kg/day.[13] The tolerance of fortified human milk can be further improved by the gradual increase to full strength fortification over a period of 3 to 4 days.

Overall, the benefits of a shorter hospital stay with decrease in hospital infections, better bone mineralization, fewer electrolyte disturbances and other potential benefits of human milk feeding strongly advocate the use of human milk with fortification for optimum growth of preterm VLBW infants.

The effects of human milk fortification on immunological factors present in human milk have yet to be finally evaluated and further studies are needed to explain this aspect of human milk fortification. Future studies should also be aimed at achieving optimum caloric intake through fortified human milk without a substantial increase in osmolality. This could be achieved by enhancing the fat content of the fortifier marginally to replace a fraction of the carbohydrates in the fortifier.

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IN SITU EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY AS A PRIMARY TREATMENT FOR URETERAL STONES

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Background: The aim of the study was to evaluate the results of extracorporeal shock-wave lithotripsy (ESWL) as a primary treatment for ureteral calculi at different levels.
Materials and Methods: We treated 166 consecutive patients with solitary ureteral stones (73 at the upper, 4 at the middle, and 89 at the lower ureter) by primary *in situ* ESWL on an outpatient basis. A maximum of three treatments were given individually before adopting ureteroscopy as an alternative treatment. The success rate was calculated on the basis of complete stone clearance and resolution of any associated obstruction. Re-treatment rates, complications and time to complete stone clearance were recorded.
Results: Complete stone clearance was achieved in 152 patients (91.6%) after an average of 10.2 days (range 1-28). The average treatment rate was 1.3 sessions per patient. As whole groups, lower ureteral stones required more treatment sessions than those in the upper ureter, and the difference was statistically significant. However, the differences in the final success rate and time to stone clearance were statistically nonsignificant. When stratified according to size, the success rate was lowest for lower ureteral stones >1 cm in diameter.
Conclusion: We believe ESWL is a safe and simple non-invasive option of choice for most ureteral calculi at different levels. Ureteroscopy represents an alternative choice in case of ESWL failure, or in cases of larger stones in the lower ureter when it might be the first option.
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Key words: Ureter, stones, calculi, extracorporeal shock-wave lithotripsy, ureteroscopy.

The natural evolution of ureteral calculi is their spontaneous passage. The adoption of a "watchful wait" involves uncertain occupational and medical outcome, especially in the military population. When a decision is made to treat this condition, most urologists offer either ESWL or ureteroscopy (URS) as primary therapy. Each of these techniques has its advantages and disadvantages, and should be considered complementary.[1] The choice in each particular case and within each hospital depends on the availability of means to perform one or the other, the efficiency of equipment, skill of the urologist, patients' preferences and cost of each treatment. We report data from our institution using ESWL as a primary therapy for ureteral stones at different levels.

Materials and Methods

TABLE 1. *Patients' age, stone size and location.*

Group	No. of patients	Age (years)	Average stone size (mm)
Upper ureter	73	35.1	8.2 (range 3-20)
Middle ureter	4	34.5	13.8 (range 5-20)
Lower ureter	89	38.9	8.7 (range 3-25)
Total	166	37.1	8.6 (range 3-25)

From September 1999 through September 2001, we treated 166 consecutive patients (160 males and 6 females) with solitary ureteral stones at different levels by primary *in situ* ESWL. Characteristics of patient age, stone size and distribution are shown in Table 1. ESWL was performed on an outpatient basis using a Siemens Lithostar Multiline lithotriptor. The energy level of the machine is measured on a scale starting from 0.1 (9.5 KV), increasing by 0.1 increments up to 1.0 (13.4 KV), then by 0.5 increments to a maximum energy level of 9 (18.2 KV). Stone localization was done by using fluoroscopy, and intravenous contrast was given when needed to aid localization of radiolucent or faintly opaque stones (6 cases). Patients with stones in the upper ureter were treated in the supine position, while a ventral prone position was used for middle and lower ureteral stones. The position of shock head in the prone position allows the shock waves to traverse only through soft tissues of the abdomen and pelvis. Sedoanalgesia, using a bolus dose of pethidine (1 mg/kg body weight) with intravenous metoclopramide (10 mg), was given just before the start of lithotripsy. Treatment started at the lowest energy level with gradual increase according to the progress of fragmentation and patient tolerance, limiting the

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TABLE 2. *Success rate in relation to the stone level and retreatments.*

Stone	After 1 session		After 2 sessions		After 3 sessions		Final success rate	
level	Patient no.	Success rate (%)	Patient no.	Success rate (%)	Patient no.	Success rate (%)	Patient no.	Success rate (%)
Upper	54/73	74	+11	89.1	+4	94.5	69/73	94.5
Middle	3/4	75	–	–	–	–	3/4	75
Lower	60/89	67.4	+15	84.3	+5	89.9	80/89	89.9
Total	117/166	70.5	+26	86.1	+9	91.6	152/166	91.6

TABLE 3. *Success rate in relation to stone level and size.*

Level	Upper ureteral stones		Lower ureteral stones	
Size	≤ 1 cm	> 1 cm	≤ 1 cm	> 1 cm
No.	57	16	77	12
Success rate	55/57 96.5%	14/16 87.5%	72/77 93.5%	8/12 66.7%

treatment to 4000 shocks per session. The bulk of cases were done by a single urologist or under his direct supervision.

Preoperative film of the kidneys, ureters and bladder and a sonogram were obtained for all patients, while intravenous urography (IVU) was done in selected cases to document the size and location of the stone, and evaluate the upper tract. Stone size was defined as the longest stone diameter as measured in the plain film of the abdomen. Patients were followed postoperatively with plain radiographs, sonograms and/or IVU on individualized intervals until they became stone free or received additional treatment. Treatment outcome was assessed by radiographic evidence of fragmentation, and success rate was calculated on the basis of complete disappearance of the stone and resolution of any preoperatively associated obstruction. Failure was designated to cases that showed no effective fragmentation or failure to pass the stone fragments after a maximum of 3 ESWL treatments. Re-treatment rates, time interval to stone clearance, and complications were recorded. Failure cases were salvaged by ureteroscopic lithotripsy. Special care was taken to collect stone material which would be enough for analysis from these failed ESWL cases. The *Z*-test was used for the statistical analysis, with level of significance at a *P* value of >1.9559.

Results

Table 2 summarizes the treatment results relative to the stone level and number of treatment sessions. Overall, complete stone clearance (success rate) was achieved in 152/166 patients (91.6%). Of the 152 patients, 8 required insertion of ureteral stents before treatment due to associated obstruction, 5 needed contrast injection at lithotripsy to help localization and 36 (21.7%) required 2 or 3 treatments before they became stone free. The average treatment rate for the whole group was 1.3±0.6 (range 1-3) sessions per patient; average power was 4.9 (15.7 KV) ±1.8 (range 1-9) and the average time to stone clearance was 10.2±7.6 (range 1-28) days. When the stones were stratified according to their size (Table 3), the lowest success rate was obtained for lower ureteral stones >1 cm in diameter.

Table 4 shows the statistical analysis of treatment results for stones in the upper and lower ureter as separate groups. Upper ureteral calculi required less average treatment sessions per patient than stones in the lower ureter, and the difference was statistically significant. The two groups, however, did not differ significantly in average stone size, average treatment power, average time to stone clearance, or final success rates. Failure cases in these two groups (13/162, 8.02%) correlated with the stone level (9/13 stones in the lower ureter) and stone size (6/13 stones were >1 cm) (Table 3). These cases were treated successfully with ureteroscopy. The stones were composed of calcium oxalate monohydrate in 7 cases, calcium phosphate in 2, mixed structure in 3, and uric acid in 1 case. No serious complications were recorded. Morbidity varied between transient mild hematuria and renal colic during passage of the stone gravels in some cases.

Discussion

In this study, we treated mainly two groups of patients with upper and lower ureteral calculi, because of the small number of middle ureteral calculi. Both groups were comparable in average stone size, but lower ureteral stones required more treatments. However, the final outcome did not differ significantly when calculated for all stones in each group. When stratified according to stone size, the success rate was considerably lower for larger stones in the lower ureter. We currently apply ureteroscopy as the primary treatment of such stones. Nevertheless, we had an overall success rate of 91.6% with no significant morbidity. These results compare favorably with other reports even for stones in the lower ureter.[2-5]

The clinical outcome of ESWL treatment of radiolucent stones did not appear to differ from that of radio-opaque ones. Intravenous contrast medium administration overcomes the problem of reduced visibility by indirectly depicting the localization of the stone. This same observation was found in other studies involving larger number of radiolucent stones.[6]

ESWL treatment of lower ureter stones is cautioned in females in fertility age. We had six females among our patients, and two of them had lower ureteral stones. One of the two was beyond her fertility age, while the other

TABLE 4. *Statistical analysis: Z-test (Z critical two-tail = 1.95996).*

	Upper ureteral calculi			Lower ureteral calculi			
	Mean	SE	SD	Mean	SE	SD	*P*-value
Stone size (mm)	8.2	0.532	4.545	8.7	0.5555	5.2401	0.7244
Treatment sessions	1.2	0.0584	0.4989	1.4	0.0671	0.6328	2.1116*
Time to clearance (days)	9.4	0.8962	7.6575	11	0.7993	7.5408	1.3305
Success	1.95	0.0268	0.2292	2.14	0.2278	2.1489	1.1470

SE=standard error; SD=standard deviation.

referred to have ESWL rather than ureteroscopy despite our caution.

The ability to predict spontaneous passage of stones has improved over the years but remains imprecise. Whilst the range of therapeutic options continues to widen, most urologists recommend either ESWL or URS for treatment of ureteral stones. Different variables influence the results of ESWL treatment, including stone size and density, ureteral obstruction, and function of the renal unit. Fernandez-Rodrigues et al.[7] found only variables of size, obstruction and function of statistical significance. In addition, other studies correlated treatment failure with ESWL voltage and stone composition, but not location or inadequate treatment.[3,8,9] A subgroup of calculi less likely to succeed could thus be identified: calculi >1 cm^2, with severe uropathy and functional annulment or delay.

The major disadvantages of ESWL are the number of repetitions often required, and the long wait until the last fragment is passed. The greater strength of URS is that it can be resolved in just one episode in up to 95% of cases, avoiding the obstructive problems that can arise after ESWL.[1] However, the stone-free success rate with URS alone depends on the location of the ureteral stone. It is highest in the distal ureter, with lesser success in the middle and proximal ureter in that order.[8,10] Although URS with holmium laser lithotripsy achieves excellent results for proximal ureteral stones 1 cm or larger, ESWL is equally efficient for stones less than 1 cm.[11]

The consensus is that ESWL therapy should remain a first-line choice in upper ureteral stones, especially if it is less than 1 cm, keeping other modalities for unfragmented stones.[11,12] For distal ureteral calculi, ureteroscopy versus ESWL continues to be a topic of significant discussion. The success rate of ESWL for distal ureteral stones varies greatly in different reports, with stone-free rates from 53%-96%, and retreatment rates of 10-30%.[2] The choice of URS as a first-line therapy for distal ureteral calculi relies on the higher success rate, less fluoroscopy time and time to achieve a stone-free state.[2,4,13,14] Ureteroscopy is also less costly than ESWL for stones at all ureteral locations.[15] The high cost of purchasing and maintaining a lithotriptor is responsible for the high treatment cost associated with ESWL. However, cost is only one of a number of important factors that are considered when determining a treatment strategy. ESWL requires less operating time, more often performed on outpatient basis, and shows a trend to less morbidity, fewer complications and quicker convalescence.[16] Thus, it seems that the total expense of both approaches is similar. Such studies support proponents of ESWL as a first choice treatment of ureteral calculi regardless the location, while saving URS as a first choice for distal obstructive calculi and those with difficult radiological study.[3,5,8,16]

Although stones in the upper ureter might respond better to ESWL treatment than those in the lower ureter, the ultimate treatment results are comparable in both clinical settings. At an institution where ESWL and URS are equally available, ESWL is still a valid safe and simple non-invasive option of choice for most ureteral calculi at different levels. Ureteroscopy represents a second choice solution in case of failure of ESWL, except in larger stone sizes in the lower ureter where it might be the first choice option.

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LAPAROSCOPIC VS. OPEN ADRENALECTOMY: EXPERIENCE AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE, RIYADH

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Background: The laparoscopic approach for adrenalectomy is now widely accepted and preferred over the conventional open approach. We describe our experience of adrenalectomy and compare the results of open and laparoscopic approach.

Patients and Methods: From March 1999 to March 2002, we performed 23 adrenalectomies. An anterior transabdominal approach was used for the open procedure, and a lateral transperitoneal approach for the laparoscopic procedure. Data from both groups were analyzed and compared.

Results: There was no difference in tumor size or pathology between the two groups. The tumor size was smaller, operative time was longer and estimated blood loss was less in the laparoscopic procedure group, however these differences were statistically insignificant. The mean length of hospital stay was shorter (5.1 vs. 9.2 days, $P < 0.01$), the mean use of postoperative narcotic analgesia was less (4.2 vs. 8.1 injections, $P < 0.05$), and the mean time for resumption of oral intake was faster (1.17 vs. 2 days, $P < 0.01$) in the laparoscopic procedure group compared to the open adrenalectomy group.

Conclusion: Laparoscopic adrenalectomy is a safe procedure that can be performed for most adrenal pathology. It is associated with faster recovery, less postoperative pain, and shorter hospital stay.

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Key Words: Adrenalectomy, laparoscopic, adrenal tumor, surgery.

Since Gagner reported the first laparoscopic adrenalectomy in 1992, there have been several reports of different approaches for laparoscopic adrenalectomy.[1] To date, there are more than 340 publications in the English literature for laparoscopic adrenalectomy, but none had made a comparison with open adrenalectomy. However, laparoscopic adrenalectomy has been reported by many as safe technique that results in quicker recovery, shorter hospital stay, less use of postoperative analgesia, and fewer postoperative complications.[2-8]

The aim of this study was to review and describe our experience in adrenalectomy at King Faisal Specialist Hospital & Research Centre, Riyadh, and to compare the results of the open versus the laparoscopic approach.

Patients and Methods

This was a retrospective study in which the medical records of all adult patients who underwent adrenalectomy at KFSH&RC between March 1999 and March 2002 were reviewed. Twenty-three adrenalectomies were performed in 21 patients. Two patients with incomplete information or lack of follow-up data were excluded from the study. Demographic data, preoperative diagnosis, size of the tumor, operative time, estimated blood loss, conversion to open, intraoperative complications, time to resume orally, postoperative use of analgesia, hospital stay and postoperative complications were reported. The patients were divided in two groups: open adrenalectomy group and laparoscopic adrenalectomy group.

All procedures were performed by a single surgeon. The open technique was anterior transabdominal approach using subcostal incision or midline in case of bilateral adrenalectomy. The laparoscopic technique involved a lateral transperitoneal approach utilizing 3-4 ports. For left laparoscopic adrenalectomy, the spleen was mobilized and

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TABLE 1. *The indications and pathology for the 21 adrenalectomies.*

Open adrenalectomy (n=9)	Laparoscopic adrenalectomy (n=12)	Total (n=21)
3 pheocromocytoma (2 bilateral in MEN 2a)	2 pheocromocytoma (1 in MEN 2a)	5 pheocromocytoma (3 in MEN 2a)
1 Conn's adenoma	5 Conn's adenoma	6 Conn's adenoma
1 benign cyst	3 benign cyst	4 benign cyst
1 myelolipoma	1 myelolipoma	1 myelolipoma
2 Cushing's (bilateral)	1 Cushing's	3 Cushing's
1 carcinoma	–	1 carcinoma

TABLE 2. *Operative and postoperative parameters in the two groups.*

	Open	Laparoscopic	*P*-value
Tumor size			
Mean±SD	6.4±4.5 cm	3.7±2.1 cm	$P<0.1$
Range	1.5-12 cm	0.6-8.1 cm	
Operative time			
Mean±SD	109±12 min	128±47 min	$P<0.2$
Range	90-128 min	65-208 min	
Estimated blood loss			
Mean±SD	240±435 ml	37.5±68.6 ml	$P<0.2$
Range	10-1200 ml	10-250 ml	
Length of hospital stay			
Mean±SD	9.2±2.8 days	5.1±1 days	$P<0.01$
Range	7-14 days	3-7 days	
Narcotic analgesic use			
Mean±SD	8.1±2.6 injections	4.2±3.7 injections	$P<0.05$
Time to resume orally			
Mean±SD	2±0.57 days	1.17±0.78 days	$P<0.01$

P-value=<0.05.

reflected medially thus exposing the left adrenal gland and superior pole of the left kidney. For right laparoscopic adrenalectomy, the retroperitoneum was opened along the attachment of the right lobe of the liver, then the liver was retracted upward, exposing the anterior surface of the right adrenal gland. Statistical analysis were performed using unpaired Student *t*-test.

Results

Twenty-one adrenalectomies were done in 19 patients. Nine were done by open procedure (7 patients) and 12 were done laparoscopic (12 patients). The overall mean age was 36 years range (13-65), and the female to male ratio was 2:1. Ten adrenalectomies were performed on the left side (3 open & 7 laparoscopic), seven adrenalectomies on the right side (2 open and 5 laparoscopic), and four bilateral (all were open). There was no significant difference in patient's age, sex, or size of the tumor between the two groups. Table 1 lists the indications and pathology for the 21 adrenalectomies performed.

The indication for bilateral adrenalectomy was bilateral pheochromocytoma and Cushing's disease. The tumor size was smaller, operative time was longer, and estimated blood loss was less in the laparoscopic procedure group, however, these differences were not statistically significant. The length of hospital stay was significantly shorter among the laparoscopic group ($P<0.01$). There was also significantly less use of postoperative narcotic analgesia among the laparoscopic group ($P<0.05$).

All laparoscopic adrenalectomies were completed except one, which was converted to open; this was a left adrenal cyst, 8.1 cm in size that opened during manipulation and collapsed and was difficult to identify the tissue planes. The pathology was benign cyst. Patients who underwent laparoscopic adrenalectomy resumed oral intake sooner than patients who had open adrenalectomy ($P<0.01$).

Table 2 shows the operative and postoperative parameters in the two groups. There were no intraoperative hemodynamic, respiratory, or surgical complications. However, two patients developed ileus secondary to pancreatitis that was treated conservatively, and the other developed respiratory complications following open bilateral adrenalectomy for Cushing's disease. We believe that this was secondary to the patient's original disease and high level of steroids resulting in weak muscle, rather than surgery related complication. There was no mortality reported among the two groups of patients.

Discussion

With the fast development of minimally invasive surgery, laparoscopic adrenalectomy has become the gold standard of adrenal surgery with several approaches.[8-11] The choice of surgical approach depends mainly on the surgeons' experience and orientation, as well as the tumor pathology, size, function, and the patient's clinical history. Initially, we started laparoscopic adrenalectomy for nonfunctioning small tumors, and later on, laparoscopic adrenalectomy became our procedure of choice for all adrenal tumors, unless there was proven or highly suspicious malignancy. This explains the lack of significant difference in tumor size between the two groups in our study. The size of the tumor for which laparoscopic adrenalectomy can be performed safely is still controversial.[12] It is the likelihood of malignancy and local invasion associated with large tumor size that make it sometimes difficult to be removed laparoscopically, not the size per se.[13,14]

The operative time was reported by some authors to be significantly longer in laparoscopic adrenalectomy, however, this was not the case in our study.[7,16] We found that the optic magnification in laparoscopy and the clarity of anatomy made the dissection and adrenal vessels control much easier and faster. The fact that most of the open adrenalectomies were selectively done for large, suspicious tumors and in patients with previous multiple abdominal surgery may account for the insignificant difference in operative time between the two groups.

The estimated blood loss was apparently more in open procedure group, however, this was not statistically significant. This may be explained by the fact that one patient with past history of multiple abdominal surgeries, had significantly more blood loss (1200 ml) in the open procedure group making the mean apparently higher than laparoscopic group.

Complications were noted in one patient in each group making it difficult to conclude any relation. However, having no major complication in the two groups may reflect that both procedures are equally safe. We found that the mean hospital stay and the use of narcotic analgesia were less in patients who underwent laparoscopic adrenalectomy. The resumption of oral intake was earlier in laparoscopic adrenalectomy group. These findings reflect the advantage of laparoscopic adrenalectomy over the open procedure and confirm previously reported observations of laparoscopic adrenalectomy being a safe procedure that can be performed for most adrenal pathologies. It is associated with faster recovery, less postoperative pain, and shorter hospital stay.[4,5,7,16]

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Review Article

RECENT ADVANCES IN VENOUS THROMBOEMBOLIC PROPHYLAXIS IN MAJOR ORTHOPEDIC SURGERY: A REGIONAL PERSPECTIVE

Hikmat Abdel-Razeq, MD

Venous thromboembolism (VTE) remains a common but preventable lethal complication following major orthopedic surgery. VTE prophylaxis has witnessed major advances in recent years. Low molecular weight heparin (LMWH) has become the agent of choice in major orthopedic procedures as elective total hip replacement (THR), hip fracture surgery and total knee replacement (TKR). Despite this, there is still some hesitation among local physicians in using MWH since it originates from pork. More recently, the issue of extended out-of-hospital prophylaxis has come up for considerable debate. Now it is widely accepted that the incidence of VTE will be lowered considerably if prophylaxis is extended to about four weeks after the procedure. Efforts to find the ideal antithrombotic agent continued, and pentasaccharides have been introduced as a prophylactic agent for patients undergoing high-risk orthopedic procedures. Multiple studies have shown promise in the superiority of these agents compared to the existing LMWH. One other major advantage of this in our local community is the fact that pentasaccharides are totally synthetic and lack any animal derivatives. In this review, we address the need and the duration for prophylactic therapy and the integration of these new antithrombotic agents in orthopedic surgery.

The Rationale

VTE is a major health problem worldwide, and pulmonary embolism (PE) is the most feared complication. One study showed that more than 50% of patients who die of PE did not receive prophylaxis despite having major risk factors and absence of contraindications to antithrombotic agents.[1] Despite overwhelming evidence of the efficacy of prophylaxis, many survey studies document wide practice variations.[2-5] Some studies show that only one-third of high-risk patients receive prophylaxis,[6] and that of those who do receive prophylaxis, one-third do not get the appropriate antithrombotic agent.[7]

Orthopedic surgery carries a high risk of VTE. Total hip and knee replacements as well as hip fracture surgeries are among the highest risk procedures. In the absence of prophylaxis, the incidence of venography-proven VTE exceeds 50%.[8-12] The incidence of symptomatic VTE is far less.[13-15] While the majority of the thrombi detected by venography are asymptomatic and will resolve without treatment, venography remains a credible outcome measure for comparing the efficacy of different prophylactic regimens.[16] Also, unrecognized and untreated deep vein thrombosis (DVT) may lead to a long-term morbidity from the postphlebotic syndrome and may predispose patients to future episodes of recurrent VTE.[17,18]

Duration of Anticoagulation

In a recent retrospective cohort study of 19,586 California Medicare patients undergoing THR and 24,059 patients undergoing TKR, the diagnosis of VTE was made after discharge in 76% of THR and 47% of TKR cases. The median time to diagnosis was 17 days for THR and 7 days for TKR.[19] This shows that limiting prophylaxis for the in-patient duration is clearly not enough, especially with recent advances in medical care with emphasis on shorter hospital stay.

Many studies have addressed the issue of out-of-hospital prophylaxis. In most of these studies, the incidence of venography-proven DVT was reduced by 50%.[20-24] In a recent meta-analysis of randomized clinical trials, Cohen et al. showed that the incidence of symptomatic VTE was decreased by 50% following extended out-of-hospital prophylaxis.[25]

Pre-Operative vs. Postoperative Prophylaxis

The timing of the first dose of LMWH prophylaxis differs among practitioners. In North America, LMWH is usually given 12-24 hours postoperatively, while in Europe, the first dose is usually given 12 hours prior to surgery. While this issue is still controversial, Hull et al.[26] in a meta-analysis showed that preoperative administration of LMWH was more effective than the postoperative approach. This same group addressed this issue in another prospective study in which patients undergoing elective THR were

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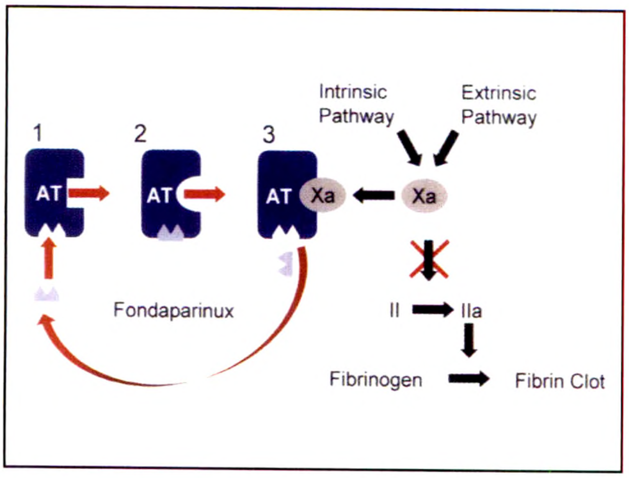

FIGURE 1. Mechanism of action for Fondaparinux. Fondaparinux {1} binds with high affinity to its binding site on antithrombin (AT). This results in {2} irreversible conformational changes, which, {3} enables it to bind and inhibit activated factor X (Xa), which is needed to activate factor II (prothrombin) to thrombin.

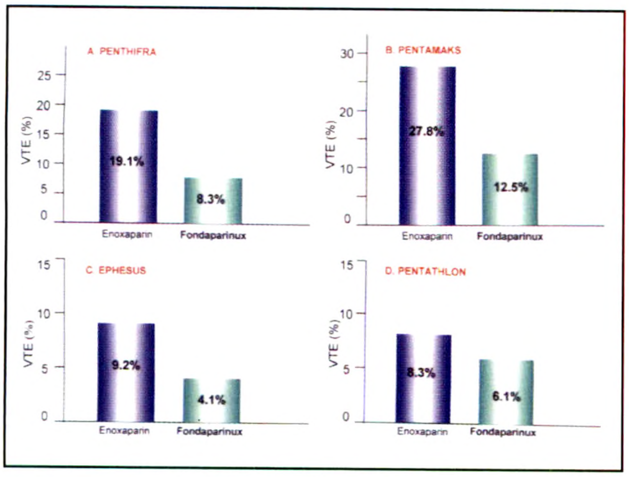

FIGURE 2. Primary efficacy results: reduction in VTE rate.

randomized to three groups: one group received Warfarin while the other two received LMWH (Dalteparin) either before or after surgery. Based on pre-discharge venography, the total and proximal DVT rates were similar among the two LMWH groups, however, preoperative LMWH caused non significant trend toward more bleeding.[24,27]

LMWH and the Risk of Spinal Hematoma

In December 1997, the FDA called attention to safety reports describing 43 patients who developed epidural, or spinal hematoma, or bleeding after receiving Enoxaparin.[28] Regional anesthesia should be avoided in patients at high risk for bleeding, and the insertion of spinal needle should be delayed for 10-12 hours after the initial LMWH injection. The whole regional anesthesia should be aborted if the aspirate was a bloody one.

The Source

All LMWH originate from pork, a fact which has resulted in delayed application of these products in our daily practice. Despite multiple randomized studies showing superior efficacy compared to unfractionated heparin, some local physicians are still reluctant to prescribe them.

Pentasaccharides

Fondaparinux (AriXtra, Sanofi-Synthelab, France) is the first agent of a new class of selective factor Xa inhibitors (pentasaccharides). This new synthetic compound with no animal-sourced components, has been designed to bind selectively to a single target in the plasma, Antithrombin III, which inactivates factor Xa, thus resulting in strong inhibition of thrombin generation and clot formation.[29,30] Figure 1 shows the site and mechanism of action of pentasaccharides.

The results of a large phase II dose-finding study suggested that a once-daily subcutaneous injection of 2.5 mg of Fondaparinux started postoperatively had the potential to significantly decrease the incidence of VTE in patients undergoing major orthopedic surgery.[31] In four multi-center, randomized, double-blinded clinical trials in patients undergoing major orthopedic surgery,[32-35] Fondaparinux was given at a dose of 2.5 mg subcutaneously once a day. The first dose was started 4-8 hours postoperatively, and the second dose was given at least 12 hours after the first one, but not more than 24 hours after the surgical procedure. In all four studies, the primary assessment for efficacy was based on a mandatory bilateral venography of the legs between day 5 and 11 or earlier if thrombosis was clinically suspected.

In patients undergoing hip fracture surgery or elective total hip replacement, PENTHIFRA[32] and EPHESUS[33], studies respectively, Fondaparinux at the above dose and schedule was compared to 40 mg of Enoxaparin once daily, started 12 hours preoperatively; a regimen widely used in Europe. While in PENTAMAKS[34] (major knee surgery) and PENTATHALON 2000[35] (elective THR) studies, Fondaparinux was compared to Enoxaparin given at 30 mg twice daily, started 12 hours postoperatively; a regimen commonly used in North America. The results of the individual studies are shown in Figure 2.

In a meta-analysis of the four studies with a total of 7344 randomized patients in more than 300 centers worldwide, the superior efficacy of Fondaparinux over Enoxaparin was demonstrated in all types of surgery (Table 1), with a reduction of 61.6%, 63.1% and 45.3% in hip fracture, major knee, and hip replacement surgery respectively (Figure 3). The superior efficacy of Fondaparinux over Enoxaparin was achieved without significant increase in the risk of bleeding.[37] Table 2 shows the difference in bleeding in both agents.

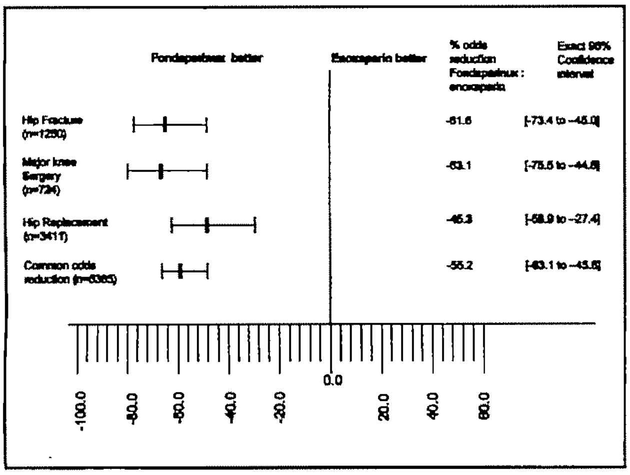

FIGURE 3. Fondaparinux's superior efficacy over Enoxaparin in all orthopedic indications (modified with permission from: Turpie et al.).

TABLE 1. *Efficacy outcomes.*

	Fondaparinux n/N (%)	Enoxaparin n/N (%)
Venous thromboembolism (primary outcome)	182/2862 (6.8)	371/2703 (13.7)
Any deep vein thrombosis	174/2677 (6.5)	363/2698 (13.5)
Any proximal deep vein thrombosis	35/2756 (1.3)	81/2775 (2.9)
Distal deep vein thrombosis only	141/2704 (5.2)	293/2709 (10.8)
Non-fatal pulmonary embolism	9/3603 (0.2)	7/3608 (0.2)
Fatal pulmonary embolism	2/3603 (0.1)	3/3608 (0.1)

TABLE 2. *Safety outcomes in orthopedic studies.*

% of patients with treatment period (up to day 11)	Fondaparinux N=3616 n(%)	Enoxaparin N=3621 n (%)
Fatal bleeding	0	1
Bleeding in critical organ	0	1
Bleeding leading to reoperation	12 (0.3)	8 (0.2)
Bleeding with a bleeding index*≥2	84 (2.3)	53 (1.5)
Wound infection	37 (1.0)	29 (0.8)
Complications at surgical site leading to prolonged hospitalization or rehospitalization	52 (1.4)	52 (1.4)
Study period (up to day 49)		
Death from any cause	48 (1.3)	52 (1.4)

*The bleeding was calculated as follows: number of units of packed red blood cells or whole blood transfused + (pre-bleeding—post-bleeding) hemoglobin (g/dL) values.

These promising results encouraged investigators to further investigate the efficacy and safety of the pentasaccharide Fondaparinux in extended out-of-hospital prophylaxis (PENTATHALON 2000 Plus Study). The initial presentation of the results were outstanding. Using venography as an end-point, the incidence of VTE was reduced from 35% to 1.4%, while clinically detected VTE was reduced from 2.7% to 0.3% (data presented at the 12th World Congress of the International Society of Orthopedic Surgery and Traumatology in San Diego, USA, August 2002).

Ongoing multiple studies are currently testing pentasaccharides in other therapeutic and prophylactic indications. The PENTALYSE study is testing the use of pentasaccharides in acute myocardial infarction, while the PENTUA study is testing it in unstable angina. At the prophylaxis level, the PEGASUS and APOLLO studies are testing it in high-risk patients undergoing general surgery, while the ARTEMIS study is testing it in high-risk medical patients. For the first time, clinicians now have access to a totally synthetic anticoagulant that is safe, and more effective than low molecular weight heparin.

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UPDATE ON INTRAPARTUM FETAL MONITORING

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Intrapartum hypoxia causes complications in about 1% of labors, cerebral palsy in 1 in 1000 pregnancies, and results in deaths in about 1 in 10,000 pregnancies.[1] Electronic fetal monitoring with cardiotocograph (CTG) which records fetal heart rate and uterine contraction pattern is standard practice during labor in most obstetric units in the developed world. The technique was introduced as a screening test in the 1970s in the belief that it would improve the detection of fetal hypoxemia and reduce cerebral palsy and perinatal mortality, particularly in high-risk pregnancies.[2]

The Fourth Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) in the United Kingdom highlighted the difficulties encountered with electronic fetal monitoring.[3] The main problems were failure to recognize CTG trace abnormalities, delay in communication and failure to take timely action. The speed with which hypoxia can develop varies with differing clinical situations and specific abnormalities of the fetal heart rate (FHR). It is also influenced by delay in delivery.[4,5] CTG traces are generally abnormal in those who develop hypoxia and acidosis in labor, and subsequent hypoxic ischemic encephalopathy,[6] although many similar traces are associated with normal outcome. Fetal blood sampling (FBS) can be used along with CTG monitoring but requires additional expertise, and is time consuming.[7] Other methods have been experimented with, but have not found widespread use. These include, fetal electrocardiography (FECG),[8] transcutaneous pCO_2 and pO_2, tissue pH[9], pulse oximetry[10] and near-infrared spectroscopy.[11] This article reviews the currently available fetal monitoring techniques in labor, with a focus on their principles, their value, limitations and acceptability in clinical practice.

Intermittent versus Continuous Monitoring

Early retrospective observational studies supported the view that CTG was superior to intermittent auscultation using either a Pinard stethoscope or a hand-held Doppler ultrasound device.[2] However, electronic fetal monitoring increased the levels of obstetric intervention—augmentation of labor, epidural anesthesia, instrumental delivery, and cesarean section consistently increased.[12] Instrumental delivery and cesarean section were even more common when electronic fetal monitoring was not backed up by fetal blood sampling.

In low-risk pregnancies, adverse events during labor that affect the development of the baby are rare. Most cases of cerebral palsy have antecedents in the antenatal period,[13] with only about 10% of cases having an intrapartum cause. It appears that electronic fetal monitoring may not be necessary in low-risk pregnancies where the fetus is at least risk from hypoxic events in labor. An admission cardiotocograph was therefore introduced to identify fetuses at risk, which needed closer monitoring during labor, allowing those with no signs of distress to be monitored by intermittent auscultation.[14] However, even this brief CTG on admission had a similar effect in low-risk women to the use of the cardiotocograph throughout labor. The intervention rate increased significantly with no effect on neonatal outcome.[15] Despite reservations against the CTG, it continues to be used routinely since the CTG trace is considered a legal document in litigation cases.[16]

The Royal College of Obstetricians and Gynecologists of the United Kingdom recommends that intermittent auscultation, using either a Pinard stethoscope or a hand-held Doppler ultrasound device, is the most appropriate method of fetal monitoring for women in labor who are low risk.[2] For this to be successful, it needs to be frequent, especially in the second stage of labor, and therefore requires one-to-one care of the woman. If intermittent auscultation identifies a problem or the woman has major antenatal or intrapartum risk factors then electronic fetal monitoring should be used. The main problem then lies in interpreting the cardiotocograph trace.

FHR monitoring during labor has a high negative predictive value, i.e., a normal pattern is reliably associated with a good fetal outcome. However, the technique has a lower positive predictive value, i.e., an abnormal pattern does not reliably predict birth asphyxia in terms of a low Apgar score and low cord artery pH.[17] The normal FHR pattern associated with a good outcome includes:

- a baseline rate of 110-150 beats per minute (bpm)
- a baseline variability (BLV) of 10-25 bpm

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- two accelerations in 20 minutes (reactive)
- no decelerations.

Methods of CTG Recording

When the membranes have been ruptured, the most accurate means of recording CTG is obtaining the fetal heart rate by means of a spiral electrode or a spring loaded electrode attached to the fetal scalp,[18] and the uterine contractions by means of placing a strain gauze on the maternal abdomen. A disadvantage of the method is that the electrode occasionally causes infection of the fetal scalp. When the membranes are intact, a non-invasive method that employs continuous Doppler ultrasound via the mother's abdomen, can be used to detect movement of the fetal heart from which the FHR is computed.

Fetal Blood Sampling

Fetal acidosis occurs in association with significant hypoxia and has two components. Accumulation of carbon dioxide leads to respiratory acidosis, while hypoxia alters cell metabolism from aerobic to anaerobic with resulting formation of lactic acid. The latter causes metabolic acidosis.

The usefulness of scalp blood pH estimations depends upon how often they are carried out. When the method is used frequently as an adjunct to CTG monitoring, proficiency in carrying it out improves, as well as the reliability of its interpretation. On the other hand, when it is performed infrequently, patient discomfort, failure to obtain a sample and poor equipment maintenance all become major problems.

PH Measurement

Studies of fetal pH associated with various FHR patterns show that some patterns have little effect on pH.[19] The patterns primarily associated with acidosis are either variable decelerations where the baseline is also abnormal or loss of FHR variability in association with decelerations. Late decelerations are predictive of significant fetal acidosis.

In the first stage of labor during which a gradual mild acidosis normally occurs, the mean fetal scalp blood pH is 7.33. A pH greater than 7.25 is therefore considered to be within the normal range. A pH between 7.20 and 7.25 requires careful surveillance and should be repeated within an hour. When the pH is below 7.20, significant acidosis exists and delivery is required. During the second stage of labor, a value as low as 7.15 may be acceptable provided normal progress in being made.

Clinical risk status, the FHR pattern, its evolution, parity of the patient, cervical dilatation and rate of progress of labor determine the need for FBS. Special attention has to be paid in those clinical situations where the fetus is likely to become acidotic faster, e.g., fetuses who are:

- growth-restricted
- preterm
- post-term
- infected
- those with thick meconium and scanty amniotic fluid.

Other factors in labor which have significant influence on the rate of decline of pH are the use of oxytocin, difficult instrumental delivery and acute events such as cord prolapse, scar rupture or abruptio placentae. In these clinical high-risk situations, the FHR pattern can become ominous in a short time. In those associated with prolonged bradycardia with no signs of recovery, and in cases with acute clinical events (e.g., cord prolapse, abruptio placentae and scar dehiscence), delivery should be expedited rather than performing FBS. Abnormalities of baseline rate, especially a gradual rise, and the reduction of the variability provide an indication for acid-base determinations by FBS. The rate of progress of labor and determination of pH at appropriate intervals may give some indication whether one could allow the labor to progress and achieve vaginal delivery in the presence of abnormal FHR pattern. Hypoxia and acidosis are unlikely in the presence of accelerations whether spontaneous or provoked and where baseline variability is normal.[20]

Lactate Measurement

Fetal lactate scalp concentrations are significantly higher in the distressed fetus compared with normal fetus. A significant correlation also exists between lactate and scalp pH, and both have similar predictive values in relation to poor fetal outcome.[21] However, it has been shown that maternal and fetal lactate concentrations increase significantly during the active stage of labor.[22] Therefore, fetal scalp blood sampling for lactate determination in the diagnosis of fetal distress should only be carried out during the first stage of labor.

Traditional methods of lactate analysis required large amounts of blood (>20 μl) for analysis and were practically not so useful. The introduction of the second-generation microvolume lactate analyzers that require only 5 μl of whole blood for analysis have overcome many of the shortcomings of the earlier techniques.[23] Lactate analysis provides only intermittent spot-check information on the condition of the fetus, which makes trend analysis difficult. However, with the small amount of blood the newer techniques require, it is easy to repeat the procedure often. If it is done within 15-30 minutes, another scalp incision is not necessary.

Fetal Echocardiography (FECG)

Fetal electrocardiographic waveform can be recorded continuously from the fetal scalp electrode used for measurement of fetal heart, and it can provide additional information on fetal responses to labor.[24] The filters used in existing CTG monitors to remove baseline noise and improve heart rate recording prevent the detection of all but gross FECG waveform changes. An increase in the ST segment and *T*-wave of the fetal ECG in response to fetal hypoxia can be expressed as a ratio of *T*-wave height to QRS height (T/QRS ratio).

It has been shown that the addition of ST waveform analysis to CTG monitoring reduces the rate of operative deliveries for fetal distress by 53%, and the use of cesarean section and rotational forceps by 74%, with no change in neonatal outcome.[8] However, the problems of obtaining high-quality FECG signals for waveform analysis remain and the technique requires further development.

Doppler Ultrasound

Color Doppler waveform analysis of fetal cerebral vessels has become an acknowledged method of measuring cerebral perfusion in high-risk pregnancies.[25] It appears that in the compromised fetus, a compensatory redistribution of blood flow to the brain takes place. Intrapartum color Doppler measurements of cerebral blood flow in cases of pathologic FHR and low fetal arterial oxygen saturation (<30%) using 3.5 MHz transabdominal transducer show an increased cerebral blood volume and blood flow mediated by an increased production of adrenal catecholamines.[26] Further understanding of intrapartum cerebral hypoxemia by color Doppler is required to assist in determining appropriate clinical management during periods of non-reassuring FHR patterns. This improvement could ultimately result in a reduction in unnecessary interventions by differentiating hypoxic fetuses from non-hypoxic and, more importantly, may lead to earlier intervention for fetuses in danger of serious compromise.

Continuous Acid-Base and Oxygenation Measurements

CTG alone is insufficient to manage fetuses in labor, and a supplementary indicator of fetal well-being is required to facilitate appropriate decision making regarding the timing of delivery for fetal compromise. In theory, this supplementary information is gained by fetal scalp blood sampling and acid-base measurement. In practice, this technique is rarely used owing to technical difficulties and lack of experience and, in most cases, decisions regarding delivery are made based on FHR patterns alone. Even where the technique is used, information is available only for the point in time when the test is performed. Because a minimum of two samples is required to establish any trend, multiple fetal incisions are required throughout labor. These issues have led to attempts to develop a user-friendly technique to monitor fetal acid-base status continuously.

Continuous pH Measurements

Earlier continuous pH monitoring systems using glass electrodes dropped out of favor because of the potential for breakage within the fetal scalp. More recent systems use a spiral needle electrode with a fiberoptic probe to detect indicator color changes associated with a change in pH.[27] Technical difficulties with calibration and application of the electrode as well as complexity of data analysis are major objections to the use of this monitoring technique. Results so far show a poor correlation between tissue and capillary pH (obtained by fetal scalp sampling) and no significant correlation between the continuous pH reading and outcome measures such as Apgar score or umbilical cord blood gas parameters at delivery.[28] However, with the appropriate technical improvements, continuous pH monitoring could be a useful tool in assessing the fetal acid-base status.

Continuous Oxygen Measurements

Fetal Pulse Oximetry

Fetal pulse oximetry has been advocated as a means of improving the specificity of cardiotocography in intrapartum fetal surveillance.[29] The technique is based on two main principles: the first is that oxyhemoglobin and deoxyhemoglobin differ in their ability to absorb light at various wavelengths, and secondly the amount of arterial blood (and hence light absorption by that blood) in tissues changes during each pulse in the cardiac cycle. It can be used earlier in labor (at cervical dilatations of ≥2 cm) than fetal scalp blood sampling (which usually requires higher dilatations).

The clinical use of fetal arterial oxygen saturation ($FSpO_2$) monitoring depends on its ability to distinguish normal from hypoxic $FSpO_2$ values in the fetus. Fetal oxygen saturation values of less than 30% have to be reached before anaerobic metabolism starts, causing a decline in pH and extracellular base excess.[10] A reference value of 30% for the fetal oxygen saturation has a good predictive value. It can be favorably compared with that of fetal blood analysis at a 7.20 threshold for fetal scalp pH. Fetal pulse oximetry may improve the specificity of fetal scalp blood sampling since $FSpO_2$ values of ≥30% have been associated with normal neonatal outcome.[30]

Although fetal oximetry has undergone numerous developments over the years, many questions still remain about its practicality, limitations and application under various clinical conditions.[10] The effective use of fetal pulse oximetry in intrapartum monitoring requires that it be applied transvaginally to an easily accessible area of the fetal presenting part (cheek or temple). The placement of the sensor should cause as little morbidity as possible to both mother and fetus. Obviously, this means of fetal monitoring would be contraindicated if the fetal presentation is too high, if the cervical os is closed or minimally dilated, or in any condition that precludes excessive transvaginal manipulation, for example, active genital tract infection, placenta praevia, or any vaginal bleeding of unknown origin. Signal artifact is an additional problem that can come from excessive fetal or maternal movement, venous pulsation and incorrect placement of the sensor.

Near-Infrared Spectroscopy

Near-infrared spectroscopy is a non-invasive procedure used for the direct assessment of fetal cerebral oxygenation during labor.[11] The technique depends on absorption by the chromophores oxyhemoglobin and deoxyhemoglobin of near-infrared light transmitted through the fetal head. Fiberoptic bundles that convey light to and from the fetal head are introduced through the cervix after it has dilated 3-6 cm after rupture of amniotic membranes. Coupling between the fiber ends and the fetal scalp is maintained by maternal tissue pressure. Thereafter, continuous bedside monitoring of changes in fetal cerebral hemoglobin concentration and oxygenation during labor are possible. Results show that FHR decelerations are associated with a fall in oxyhemoglobin and a rise in deoxyhemoglobin, indicating cerebral desaturation.[31]

Unlike pulse oximetry, near-infrared spectroscopy is not dependent on the presence of an arterial pulsation. In addition, as an optical method it does not require electric coupling with the skin. However, difficulties with equipment maintenance and data interpretation have prevented the widespread use of this technique in labor wards. More refinements are required before near-infrared can be used to supplement CTG and scalp blood pH monitoring.

Continuous pCO2 Monitoring

The method involves measuring partial pressure of carbon dioxide (pCO_2) transcutaneously using an electrode that is essentially a pH electrode with a membrane permeable to carbon dioxide. The electrode is fixed to the fetal scalp using glue or suction after rupture of the membranes. Studies show a positive correlation between the transcutaneous pCO_2 and the fetal blood pH.[32] The technique may be useful in excluding fetal acidosis in cases where fetal distress is suspected from the CTG pattern. However, the procedure has not been widely used because electrode application is time consuming, reapplication is difficult, and patient discomfort is a major concern.

Combined Continuous Monitoring Methods

The procedure involves using mass spectrometry to measure continuous transcutaneous partial pressure of oxygen (pO_2) and transcutaneous pCO_2 simultaneously.[33] During late decelerations, pO_2 levels fall whereas pCO_2 levels increase. However, accurate measurement of the gases is hampered by problems of diffusion and fetal head compression as well as electrode application. Transcutaneous pO_2 and pCO_2 are, therefore, not so useful for continuous fetal monitoring in labor. Similarly, combined continuous pH and pCO_2 monitoring methods have enjoyed limited success because of a lack of a user-friendly tissue pH electrode.[34]

Fetal Hypoxia and Timing of Delivery

The pathogenesis of intrapartum hypoxia is often multifactorial but poorly understood. Processes such as uteroplacental vascular disease, reduced uterine perfusion, fetal sepsis, reduced fetal reserves, and cord compression can be involved alone or in combination, and gestational and antepartum factors can modify the fetal response.[35] Methods of screening and diagnosing the condition have limitations. Thus, when the condition is thought to be present, diagnosed clinically as "fetal distress," clinicians aim for a swift delivery (within 30 minutes) because they lack a clear understanding of the severity of the hypoxia.

In theory, the speed with which hypoxia develops and the ability of the fetus to withstand this insult vary and are difficult to quantify. For example, sudden and profound hypoxia such as which occurs with placental abruption or vasa praevia probably requires delivery within 10 minutes if death or serious disability is to be avoided. In contrast, if the hypoxic insult is more slowly progressive (as it usually is), delivery within 30 to 60 minutes is unlikely to result in serious harm. In such cases, the usual threshold for intervention is a fetal scalp pH of <7.20, yet serious neurodevelopmental disability probably occurs only when the pH is <7.00.[36]

Conclusion

Although the advent of CTG monitoring has radically changed the practice of intrapartum fetal surveillance, problems associated with its use remain. These include low specificity (and consequent increased operative intervention rate), difficulty in interpretation and inter-individual variations in interpretation. Despite strong evidence against the routine use of electronic fetal monitoring, its use continues since the cardiotocograph has become an important legal document in obstetric litigation cases. Nonetheless, obstetricians must use electronic fetal monitoring appropriately in high-risk women, and recognize intermittent auscultation as a valid form of management for low-risk cases.

To improve the specificity of CTG, efforts have focused on the development of alternative fetal monitoring techniques. Fetal scalp blood sampling was developed in an attempt to improve the predictive value of CTG, but the technique is cumbersome and not widely used. Management decisions are still frequently made using FHR patterns alone.

Continuous biochemical measurement of fetus including continuous pH, pO_2, or pCO_2 and various combinations of these methodologies have not found widespread use in clinical practice, mainly owing to technical problems and difficulties associated with the continuous direct measurement of these parameters in fetal blood throughout labor. Nonetheless, Doppler ultrasound, fetal pulse oximetry, and near-infrared spectroscopy have the potential to provide critical information relating to the detection and management of the hypoxic fetus.

The goal of intrapartum surveillance and its further development is better patient care for both the fetus and the mother. For optimal results, electronic fetal monitoring has to be used appropriately and adequate knowledge to interpret traces is essential. Exceptions should be acknowledged and the clinical picture should be incorporated into the interpretation. The newer tools such as fetal pulse oximetry and fetal electrocardiography may be useful as an adjunct to electronic monitoring. Further research is needed to develop more specific tests of fetal well-being that will identify babies at risk during labor without having a major impact on women.

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WHAT'S YOUR DIAGNOSIS?

Submitted by Faisal Al Mane, FRCPC, MRCPI; V. Thomas, FRCP;
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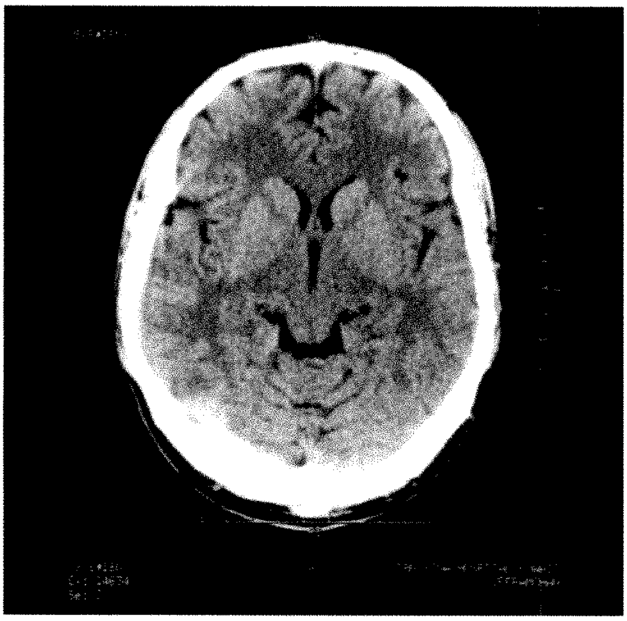

FIGURE 1: Non-enhanced CT scan of head.

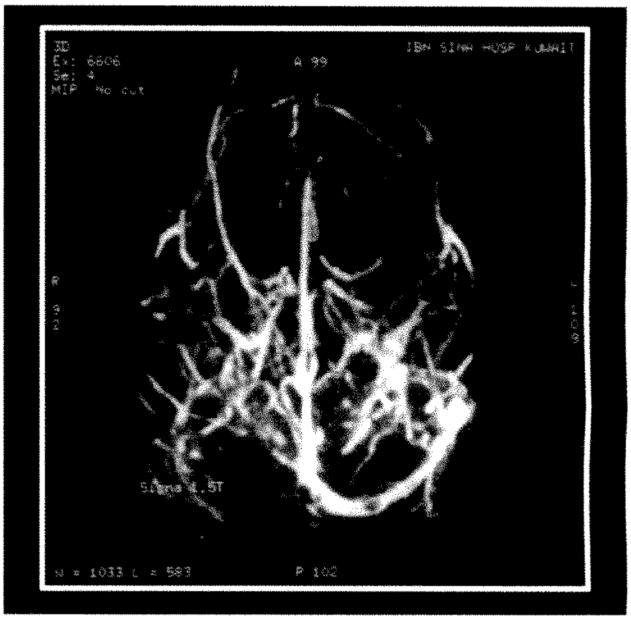

FIGURE 2: 2D/time of flight (TOF) magnetic resonance venography (MRV).

History

A 36-year-old male patient presented with headache and occasional vomiting of two months' duration. The patient had no underlying medical illness, and his clinical history was unremarkable. His physical examination showed bilateral papilloedema, otherwise, it was unremarkable.

1. What abnormality can be seen in Figure 1?

2. What abnormality can be seen in Figure 2?

3. What's your diagnosis?

ANSWER TO WHAT'S YOUR DIAGNOSIS?

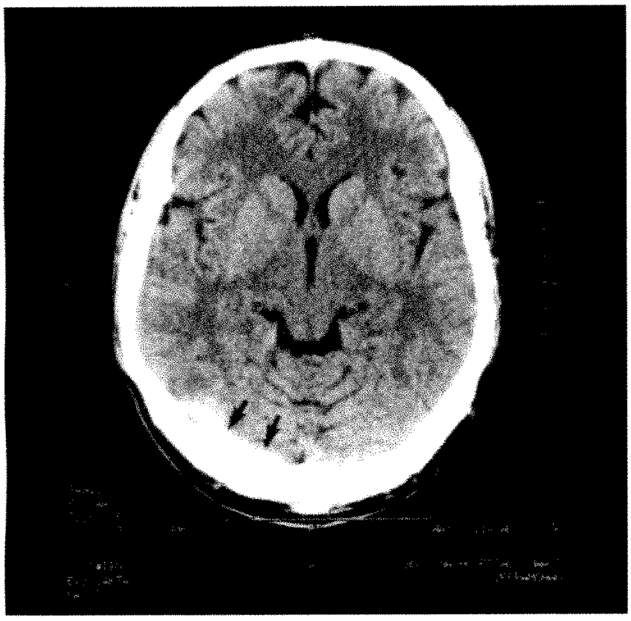

FIGURE 1. Axial non-enhanced CT of the brain demonstrating hyperdensity in the right transverse sinus, suggestive of sinus thrombosis.

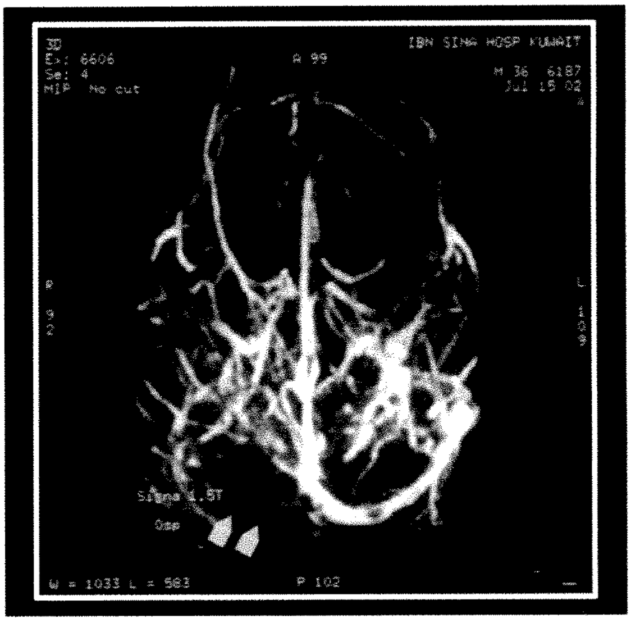

FIGURE 2. MR venography. Collapse axial view demonstrating lack of flow enhancement in the right transverse sinus, confirming the venous sinus thrombosis.

Diagnosis: Right transverse sinus thrombosis.

Discussion: Cerebral venous sinus thrombosis (CVST) is an uncommon condition which is being diagnosed more frequently recently due to greater awareness and the availability of better diagnostic techniques. Predisposing factors for CVST include:

- infections: paranasal sinusitis, intracranial infections
- trauma: head trauma, neurosurgical interventions
- Medical and surgical conditions: dehydration, pregnancy and purperium, disorders of coagulation, hematological disorders: (polycythemia rubra vera, sickle cell disease, thrombotic thrombocytopenic purpura, and paroxysmal noctural hemoglobulinuria); malignancies; collagen vascular disease including SLE, Wagner's granulomatosis, Behcet's disease.
- Medications such as oral contraceptives and hormone replacement therapy.

The clinical presentation of patients with DVST depends on the location and extension of the thrombosis and the presence of collateral pathways (superior sagittal sinus, transverse sinus, straight sinus, cortical verses deep venous system).

The symptoms could be nonspecific such as headache and vomiting, lasting for hours or days. These symptoms are due to increased global venous pressure. Other symptoms include double vision, blurred vision, altered consciousness and seizures. It can also manifest with papilloedema, focal neurological deficits, cranial nerve palsies and nystagmus. The progression of clinical symptoms and signs is slow, extending over a period of days or weeks. The crescendo progression of clinical features should alert the physician to the diagnosis of CVST. Simultaneous veno-occlusive disease can occur in other parts of the body, with pulmonary embolism occurring in 11% of patients with CVST.[1]

The investigation of a patient presenting with symptoms and clinical signs suggestive of CVST should focus on establishing the diagnosis and searching for the underlying cause. CT scan is used as the first imaging modality, simply because of its wide availability, and also to exclude other conditions such as intracerebral hemorrhage or abscess. On plain CT, a clot may be demonstrated as an elongated area of high attenuation in the transverse or straight sinus (cord sign), whereas on contrast-enhanced CT, a superior sagittal sinus thrombosis will appear as a triangular defect (empty delta sign) which is present in 10%-20% of cases.[2]

If the venous cerebral ischemia is prolonged, hemorrhagic conversion occurs and it becomes readily visible on plain CT. Magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) have largely replaced invasive cerebral angiography for the diagnosis of CVST. Most MRV methods are either phase-contrast (PC) or time-of-flight (TOF) techniques. It has been suggested that MRV with phase-contrast technique provides rapid and overall, better imaging of the intracranial venous sinuses as compared to the TOF technique.

There are few therapeutic trials in CVST. The antithrombotic treatment would include hepatic, thrombolysis and oral coagulation. Two randomized trials have looked at the benefit of heparin in patients with CVST. One of the first studies (randomized blinded placebo-controlled) in 20 patients with aseptic cerebral venous sinus thrombosis concluded that anticoagulation with dose-adjusted intravenous heparin was an effective treatment, and that associated intracranial hemorrhage was not a contraindication for its use.[3] The second more recent randomized trial compared low molecular weight heparin with placebo for the treatment of CVST. This trial failed to demonstrate any benefit for heparin. However, the study confirmed that there was no significant increased risk of hemorrhage with heparin.[4] A meta-analysis of the two trials showed a relative risk reduction with heparin of 70% in death and 56% for death or dependency.[5,6] Based on these trials, intravenous heparin should be considered as first-line treatment even in the presence of hemorrhagic infarction.

If the clinical picture continues to worsen while the patient is receiving heparin, thrombolytic therapy should be considered. Other groups of patients in whom thrombolytic therapy should be considered include those with rapidly progressive thrombosis that involves large parts of the cerebral and venous system with diffuse brain swelling. Thrombolytic therapy can be given either as a systemic intravenous infusion or delivered locally into the dural sinus via direct percutaneous or retrograde transverse approach.[6] Most investigators also suggest oral anticoagulant following the treatment of the acute phase for 3-6 months, except where there is a known prothrombotic condition in which treatment may have to be life long.[7]

The overall outcome of CVST is variable. The majority of patients recover with minimal disability. A recent study by the Dutch Venous Sinus Thrombosis Study group looked at both mortality and prognostic factors and found mortality to be in the range of 10%, and poor outcome at 12 weeks was associated with patients presenting with papilloedema, coma or altered level of consciousness, age >33 years and intracerebral hemorrhage.[8]

Initial investigations of our patient were normal, including anticardiolipin antibodies and lupus anticoagulant antibodies. Further investigations for hypercoagulable state are underway. The patient was treated initially with intravenous heparin and later with warfarin. If hypercoagulable state is diagnosed, the patient might need life-long warfarin therapy.

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Special Communication

THE INFLUENCE OF ACADEMIC STRESS ON FREE RADICALS PRODUCTION IN THE BLOOD OF STUDENTS DURING EXAMINATIONS

Laila Y. Al-Ayadhi, PhD

Phagocytes are the first line of defence against invading pathogens, killing and disposing of them with impressive efficiency. Neutrophils and other phagocytes manufacture O_2 (superoxide) by the one-electron reduction of oxygen at the expense of NADPH (nicotinamide adenine dinucleotide phosphate). Most of the O_2 reacts with itself to form H_2O_2 (hydrogen peroxide). From these agents a large number of highly reactive microbicidal oxidants are formed, including HOCL (hypochlorous acid), which is produced by the myeloperoxidase-catalyzed oxidation of Cl by H^2O_2;OH (hydroxyl radical), produced by the reduction of H_2O_2 by Fe ++ or Cu +; ONOO (peroxynitrate), formed by the reaction between O_2 and NO; and many others.[1] These reactive oxidants are manufactured for the purpose of killing invading microorganisms, but they also inflict damage on nearby tissues, and are thought to be of pathogenic significance in a large number of diseases. The hormones and other physiological agents that mediate the effect of stress on the body have protective and adaptive effects in the short run and yet accelerate pathophysiology when they are over produced. Acute stress enhances immune function whereas chronic stress suppresses it.

Mease et al. in 1998, showed in a study conducted in the US examining the effect of final examination on the immune response in healthy and asthmatic adolescents, that during examination periods, all students showed significant immunological alteration from baseline. Natural killer cell activity was significantly lower, whereas lymphocyte proliferation and neutrophil superoxide release were significantly higher.[2] These immune changes tend to return toward baseline during the post-examination period, but the enhanced neutrophils reactivity continued to rise.[3] Furthermore, it was concluded that academic examination stress induces significant hematological changes indicative of an increased number of RBC and increased hemoglobinisation.[4] It was also demonstrated that academic stress significantly increased Ht, Hb, MCV, MCH and MCHC levels, and significantly decreased red blood distribution.[2] In addition, Deinzer et al. demonstrated a positive correlation between academic stress and the development of peridontal inflammation, bleeding gums and deterioration in gingival health.[5]

The above evidence suggests that long– and short-term stress induce an alteration in the immune response and hematological indices through most probably a neuroendocrine mechanism. The aim of the current study is to examine the effect of academic stress (examination stress) on the function of isolated humane polymorphonuclear (PMN) leukocytes in first-year medical student at King Saud University.

Subjects and Methods

Eighteen healthy first-year medical students participated in this study; all had no active disease and were not on any medication. Informed consent was taken from each subject and blood samples were taken on three different occasions: 4-6 weeks before examination; during the examination week; and 4-6 weeks after the examination. Blood samples were then processed as follows:

Separation of PMNs

Isolation of polymorphoneuclear leukocytes (PMNs) was carried out as previously described by Al-Tuwajri et al.[6] Briefly PMNs were separated by using neutrophils isolation medium (NIM) (Cardinal and Associates, USA). Fresh blood was collected by venipuncture in sterile containers with heparin (10I U/mL, Fischer Scientific Co., NJ). Ten millilitres of heparinized blood was mixed with 1 mL of 6% (w/v) dextran T500 in saline solution (0.9%, w/v Nacl in H_2O) in a 15 mL tube and then incubated for 30 min at room temperature. The leukocyte-rich plasma was layered over 3 mL Nycodenz solution in a 12 mL tube and centrifuged at 1800 rpm for 15 min in a Heraeus centrifuge (Model GmbH, Osterode). Ten millilitres of phosphate-buffered saline (PBS) (Electronucleonics Inc., Columbia, MD) was added to the bottom PMNs-rich portion and centrifuged at 1700 rpm for 10 min. The supernatant was discarded and the sediment suspended with 5 mL of NH4Cl

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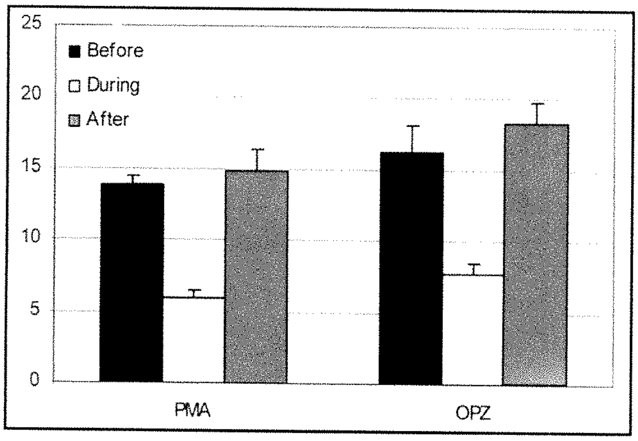

FIGURE 1. The effect of academic stress on luminal-dependent CL response of whole blood stimulation with PMA and OPZ. The graph shows a reduction in oxygen free radicals production during examination time compared to period before and after the examination. The changes were statistically significant ($P<0.001$). Data expressed as mean ±-SEM.

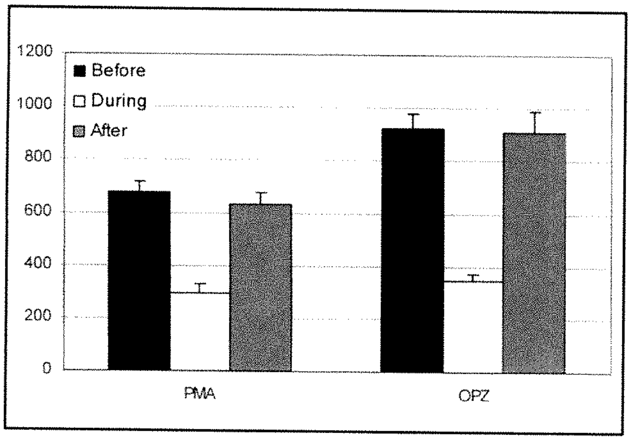

FIGURE 2. The effect of academic stress on luminal dependent CL response of polymorphoneuclear stimulation with PMA and OPZ.

(0.87%) and left to stand in ice for 10 min to lyse erythrocytes. The cells were then centrifuged as above and resuspended in 1 ml of PBS. The PMNs were counted and viability determined by Trypan blue (0.2%) exclusion test. Only PMNs whose viability was above 90 % were used in the experiments.

Phorbol myristate acetate (PMA) (Sigma Chemical Co., USA) was dissolved in DMSO to give a stock solution of 2 mg/mL. This stock solution was stored at -20°C till used. The stock solution was further diluted to 2 ng/mL with PBS prior to use. Luminal (Sigma Chemical Co.,USA) was dissolved in DMSO to give a concentration of 10 M.

To prepare opsonized zymosan (OPZ), particulate zymozan was washed twice and resuspended in PBS and the concentration adjusted to 12.5 mg/mL. Opsonization was performed by incubating 100 µl of autologous human serum from healthy individuals and 900 µl of zymosan suspension at 37°C for 30 min, washed with PBS and then resuspended in PBS to give a final concentration of 1.25 mg/mL. OPZ was used to stimulate PMNs.

Measurement of Oxygen-Free Radicals by Chemiluminescence

An LKB Wallac 125 luminometer with a constant temperature 37°C controller (Wallac Oy, Finland) connected to an Apple II computer, as described by Tono-Oka et al.[7] was used. The principle of oxidation of luminal (5 amino-2, 3-dihydro-1, 4-phthalazinedione, a cyclic hydranized) by reactive oxygen species produced during phagocytosis in phagocyte cells was employed to increase the amount of measurable light. Oxygen production was measured by luminal-dependent CL. Hydrogen peroxide production was measured by luciginin-dependent CL. Both measurements were done using LKB (Wallac) luminometer. Results were analyzed for significance using the two-tailed Student's *t*-test. Results were considered significant when $P<.001$.

Results

Production of Oxygen-Free radicals

Academic stress caused a marked inhibitory effect on luminal-dependent CL response of isolated human whole blood. CL peak response during the pre-examination period was 13.82±-0.62 (PMA), and 16.3±-1.8 (OPZ). During the examination period, CL response reduced to 6.02±-0.5 (PMA) and 7.75±-0.7 (OPZ). This was a reduction of 43.5% and 47.5%, respectively, and both were significant ($P<0.001$)(Figure 1). This inhibition was abolished in the post-examination period. Results also showed a marked inhibitory effect on luminal-dependent CL response of isolated human PMNs during examination period. CL peak response during the pre-examination period was 676.7±-40 (PMA), and 919±-60 (OPZ). During the examination period CL response reduced to 297.9±-31 (PMA) and 345.6±-25 (OPZ). This was a reduction of 56.19% and 37.6%, respectively, both being significant reductions ($P<0.001$), (Figure 2). This inhibition was abolished in the post-examination period. In addition, there was an increase in the reactivity of whole blood and PMN cells to stimuli such as luminal and ludignine during exam time.

Production of Superoxide

Examination stress caused a marked inhibitory effect on luciginin-dependent CL response of isolated human whole blood. CL peak response during the pre-examination period was 10.33±-1.5 (PMA), and 13.66±-1.69 (OPZ). During the examination period, CL response reduced to 4.34±-1.3 (PMA) and 6.2±-0.7 (OPZ). This was a reduction of 42% and 45.38%, respectively, which was significant ($P<0.001$) (Figure 3). This inhibition was abolished in the post-examination period.

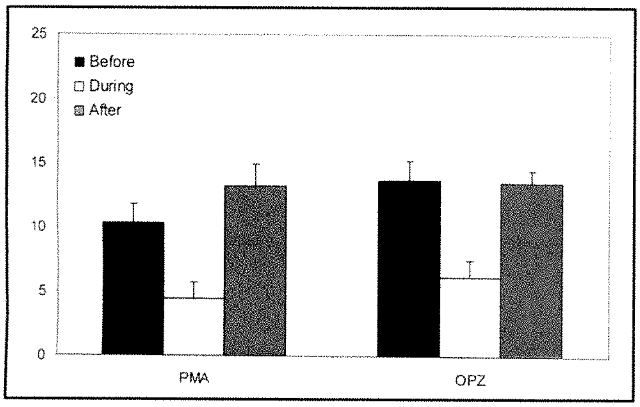

FIGURE 3. The effect of academic stress on lucigigine dependent CL response of whole blood stimulation with PMA and OPZ.

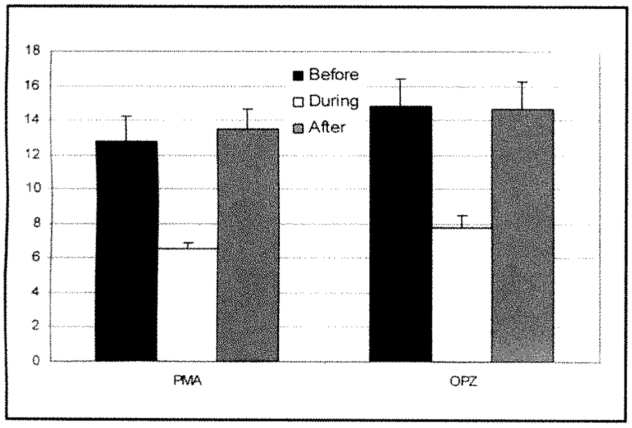

FIGURE 4. The effect of academic stress on luciginine dependent CL response of polymorphoneuclear stimulation with PMA and OPZ.

pre-exam period was 12.8±-1.4 (PMA), and 14.78±-1.6 (OPZ). During the examination period, CL response reduced to 6.5±-0.4 (PMA) and 7.76±-0.7 (OPZ). This was a reduction of 50.78% and 52.5% respectively, both of which were significant (*P*<0.001). This inhibition was abolished in the post-examination period (Figure 4).

Discussion

Whole blood and PMNs obtained from the medical student in this study showed a significant reduction in free radicals production in the exam period compared to the pre-exam period. Those changes were abolished in the post exam period. In previous studies, scientist concluded that although psychological stress altered the immune response, these changes have generally been small and within normal ranges.[8] On the contrary, results from our study showed a change, which was statistically significant.

High levels of chronic stress have been associated with an increased susceptibility to infectious diseases. Previous reports evaluating academic stress or other similar life stressors on neuroendocrine system reported conflicting results. Our results indicated a reduction in reactive oxygen species production, which was significant, during the exam period. This in turn indicates a reduction in the phagocytic activity of whole blood and in particular PMN cells. This reflects indirectly a reduction in the ability of the immune system to get rid of any pathogens in the body. This might explain the susceptibility of the body to infection during examination, for example, sore throat, runny nose and gastroenteritis. In the post exam period, PMN and whole blood CL response went back to normal, which indicated that the factors which resulted in reduction in ROS production during exam period disappeared in the post-exam period.

Various stressors also affect immune function, for instance, restraint stress decreased phagocytosis by neutrophils[9] and macrophages,[10] natural killer cell activity, and radical scavenger activity.[11] It is generally accepted that neutrophils play an important role in the host defense against infectious agents,[12] either alone or in cooperation with immunoglobulin and complements, and destroy them with toxic agents such as reactive oxygen and lysosomal enzymes. It is well known that phagocytosis and reactive oxygen production of neutrophils are altered by exercise and stress. Many investigators have reported the effect of exercise or stress on neutrophils function in humans and animals.

In this study, the effect of academic stress on neutrophils function was demonstrated. Our results showed a decrease in neutrophils activity through a reduction in the oxygen free radicals production during exam time, which recovered in the post exam period. Impairment of immune response has been associated with repeated or prolonged stress.[9] Particularly in severely stressed conditions, immune reactivity could be down regulated to a point that provides inadequate protection to infection or cause autoimmunity. It will be very interesting to measure, in addition, plasma levels of noradrenalin, adrenaline, cortisol, ACTH and other stress-related hormones to find the true cause for this reduction in the oxygen free radicals production.

The other interesting finding was the difference in reactivity of PMNs cells to stimuli such as PMA and OPZ. The marked reduction of time to peak chemiluminescence response during the exam time compared to pre-exam period was significant and indicative of reduction in the responsiveness of PMN cells to stimuli such as microorganisms and other pathogens. This, in addition, supports our finding of reduction in CL response and in turn reflects a reduction or delayed phagocytic function of PMN cells, which can explain the increased susceptibility to infection during exam time.

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CONGENITAL ANEURYSM OF THE PULMONARY ARTERY: CASE REPORT AND LITERATURE REVIEW

Abdullah A. Assiri, MD; Ziad R. Bulbul, MD

True congenital aneurysms of the pulmonary arteries are very rare. Usually, they are associated with congenital heart disease. When no other lesions are present, the condition is referred to as idiopathic pulmonary artery aneurysm. Occasionally, aneurysms are found accidentally. Early surgical intervention is crucial to avoid airway compression and ensuing complications.

Case Report

A six-week-old female infant, a product of a full-term pregnancy, was admitted at the age of two days to a local hospital, with marked respiratory distress and poor feeding. The oxygen saturation was 80% in room air. Chest x-ray showed moderate cardiomegaly. She was mechanically ventilated for one week and transferred to our institution for further evaluation and management.

Physical examination revealed moderate respiratory distress at a rate of 50/min. and a heart rate of 130/min. Room air oxygen saturation was 88%. Cardiac auscultation revealed a single-second heart sound and a grade II/VI systolic murmur at the left upper sternal border. Chest examination revealed diminished air entry bilaterally with mild expiratory rhonchi. The liver was 2 cm below the right costal margin. The peripheral pulses were normal.

Electrocardiogram showed sinus rhythm and right ventricular hypertrophy. Chest x-ray showed moderate cardiomegaly and a prominent pulmonary artery with generalized hyperinflation of the lungs. Echocardiogram revealed dilated right ventricular outflow tract, and pulmonary valve annulus measuring 19 mm. Aneurysmal dilatation of the main, as well as proximal right and left pulmonary arteries measuring 30, 25 and 17 mm, respectively, was noted (Figure 1). The Doppler gradient across the pulmonary valve was only 20 mm Hg. Significant pulmonary regurgitation was noted. The right ventricular function was moderately impaired. There were no associated congenital heart lesions.

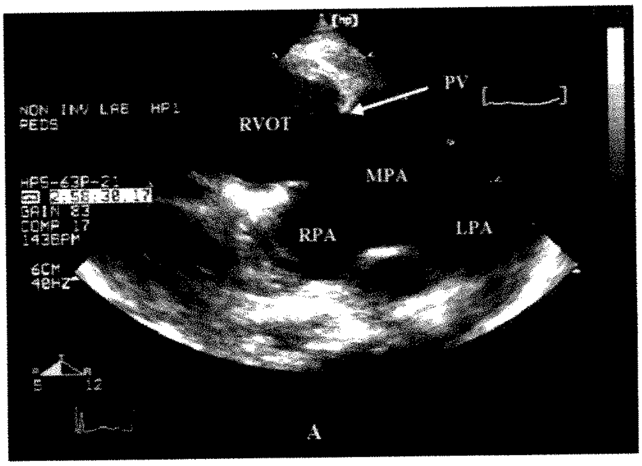

FIGURE 1. A two-dimensional short-axis parasternal view showing the aneurysm of the main, right and left pulmonary arteries. Note the dilatation of the pulmonary valve annulus.

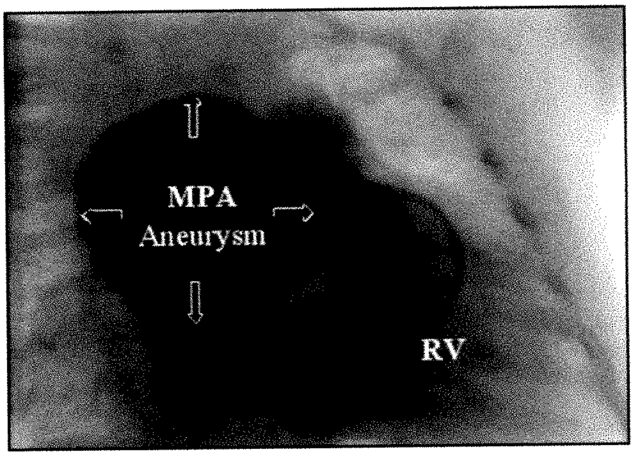

FIGURE 2. Right ventricular angiogram showing the large aneurysm of the main pulmonary artery.

Cardiac catheterization was done to verify diagnosis. Hemodynamic data showed mean right atrial pressure at 11 mm Hg. The right ventricular pressure was 71/10 mm Hg. Simultaneous aortic pressure of 90/70 (mean of 75 mm Hg) was recorded. Aortic oxygen saturation was 82%. Right

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ventricular angiogram showed a dilated chamber with poor function. The right ventricular outflow tract was severely dilated. Selective angiograms showed large aneurysms of the main, right, and left pulmonary arteries (Figure 2). The ascending aorta and the right superior vena cava were compressed by the dilated pulmonary arteries. Neither a patent ductus arteriosus nor other congenital defects were seen angiographically.

The patient was operated on the following day. The pericardium was opened through a median sternotomy. A very large aneurysm of the main pulmonary artery and its proximal branches was found. The pulmonary valve was bicuspid with a dilated annulus. Resection of the aneurysm and pulmonary annuloplasty was performed with no operative complications.

Microscopic examination of the specimen revealed myxoid degeneration. The patient had smooth postoperative course and was discharged from hospital on the sixth postoperative day. At six months follow-up, the patient was doing well. Echocardiogram showed a mildly dilated right ventricle and main pulmonary artery. Both pulmonary artery branches were of normal size. The right ventricular function was normal.

Discussion

Isolated, idiopathic pulmonary artery aneurysms are rare.[1] Aneurysms may also be found in association with other conditions like congenital heart disease,[2] pulmonary shunts,[3] syphilis, degenerative changes in the arterial wall, trauma, pulmonary hypertension, and Marfan syndrome. Congenital heart diseases include patent ductus arteriosus, pulmonary valve stenosis and insufficiency.[1,2,4,5] The incidence of idiopathic pulmonary artery aneurysms has been estimated to be 7/100,000 live births.[2] Patients may present with symptoms related to the aneurysm or may be discovered incidentally.[6] The early presentation of our patient and the absence of associated lesions support its congenital nature. Angiography is the standard tool for diagnosis.[7] Contrast-enhanced CT scan is helpful in showing the size and extent of the aneurysm.[8] Once the diagnosis has been made, surgery should be performed to avoid serious complications.[9]

Fatal outcome from pulmonary artery aneurysms is not unusual, especially when associated with pulmonary hypertension.[9] Different surgical approaches have been proposed and include the use of prosthetic replacement,[10] resection and replacement with valved conduits, and aneurysm resection with end-to-end anastomosis. To our knowledge, this is the youngest patient ever reported with a congenital pulmonary artery aneurysm where aneurysm resection, primary anastomosis and pulmonary valve annuloplasty were done successfully.

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BRONCHOPULMONARY MUCOID IMPACTION (BRONCHIAL CASTS)

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Significant mucoid impaction has been described with asthma, allergic bronchopulmonary aspergillosis,[1,2] cystic fibrosis,[2,3] bronchial atresia with intrapulmonary sequestration,[2,4] and endobronchial lesion[2,5] with post-obstructive mucoid impaction. Some case reports have shown an association with endotracheal intubation[6] and transtracheal oxygen catheter insertion,[7] and also in children with cyanotic heart diseases.[8]

Only a few case reports of mucoid impaction of unknown etiology are described in the literature. To the best of our knowledge, ours is the first case report in the Kingdom of Saudi Arabia. In our patient, a careful assessment of past medical history and the ensuing work-up ruled out asthma, allergic bronchopulmonary aspergillosis and other secondary causes of pulmonary mucoid impaction, thus establishing the diagnosis of mucoid impaction of unknown etiology.[8] The mucus casts which have been described as "bronchial cast" or "plastic bronchitis" are the obstructive plugs that form in the bronchial tree.[9] They may vary in size from small segments to complete casts of an entire lung. The expectoration of a large cast is a dramatic clinical finding and the condition consequently attracts attention out of proportion to its rarity.[10,11]

Case Report

A 20-year-old female was referred to our hospital with a one-year history of productive cough and exertional dyspnea. Chest x-ray showed left parahilar mass and persistent bilateral lower lobe infiltrates, which were not responding to multiple courses of antibiotics and to the empirical anti-tuberculous (TB) treatment. Her past history was significant only for 15 mm PPD skin test. Other examinations were unremarkable.

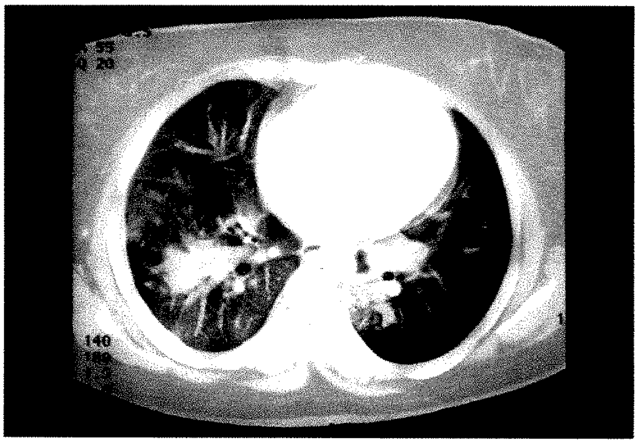

FIGURE 1. CT chest on initial presentation. Bilateral lower lobes infiltrate and left parahilar density.

Laboratory Data

Investigations were significant for esonophilia of 1000 IL. Renal profile and other laboratory data were within normal limits. Sputum culture and sensitivity were normal. Chest x-ray showed bilateral lower lobe infiltrates and left parahilar density. Chest CT scan confirmed the chest-x-ray findings (Figure 1). Pulmonary function tests were within normal limits.

After initial workup, the patient underwent fiberoptic bronchoscopy, which revealed thick whitish secretions impacted in the right lower lobe, left upper lobe and left lower lobe bronchus, which proved difficult to be removed by the bronchoscope, prompting a follow-up rigid bronchoscopy to be performed. Endobronchial biopsy showed submucosal infiltration of eosinophils. The mucus plug contained masses of eosinophils and Charcot-Leyden crystals arranged in a laminated pattern. No organisms were found. Aspergillus antibody and skin test were negative with normal IgE levels, and stools for Ova and parasites were negative. Post-bronchoscopy chest x-ray and chest CT showed dilated airways and reduction of RLL infiltrate (Figure 2). Because of peripheral eosinophilia, eosinophils in mucus plugs, eosinophilic infiltration in endobronchial biopsy, and a negative work-up for pulmonary infection,

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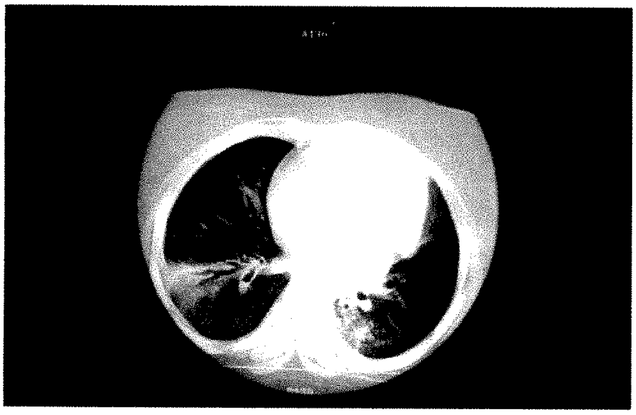

FIGURE 2. Post-bronchoscopy. CT chest shows cleared of infiltrates and dilated airways.

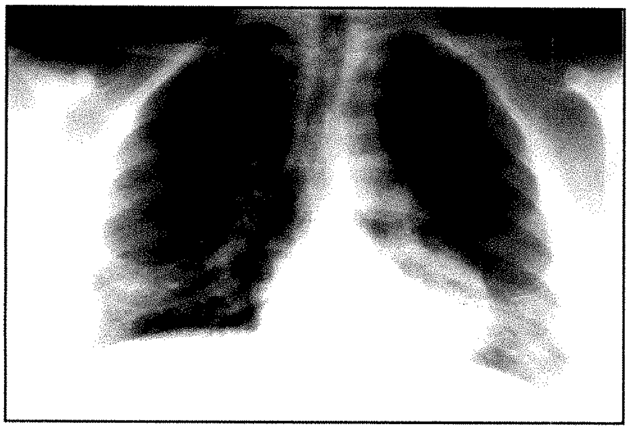

FIGURE 3. Follow-up CXR after four weeks. Steroid treatment shows complete resolution of lung infiltrates.

the patient was given a course of prednisone starting with 40 mg and tapering off in six weeks.

The patient was seen in a follow-up visit after 12 weeks. She was asymptomatic with complete resolution of the lung infiltrate and a reduction in the size of bronchi (Figure 3).

Discussion

The first report of a bronchopulmonary mucoid impaction is attributed to Galen,[12] who described a case and thought the cast was a collection of blood vessels ("venae arteriosae exprectorati"). The subsequent literature contains a confusion of terms that changed with time: bronchial polypi, bronchitis pseudomenbranosa,[12] fibrinous bronchitis,[13] and plastic bronchitis.[14] More recently, the term "mucoid impaction" has been used.[15] These casts are classified into two groups: type 1, inflammatory, consisting of casts composed mainly of fibrin and dense eosinophilic inflammatory infiltrate; and type 2, acellular casts consisting of mucin with a few or no cellular infiltrate (almost exclusively found in children with cyanotic heart diseases).

In most cases of bronchial casts or mucoid impaction, patients end up with wrongful thoracotomy and lung resections, but awareness of this condition, and radiological and bronchoscopic findings could help avert unnecessary diagnostic and surgical intervention.[3,4,14,15]

Although no definitive pathophysiology of this entity is known, in some case reports, a problem with ciliary clearance of mucus or excessive mucus production has been speculated,[6] but the presence of eosinophils and Charcot-Leyden crystals in mucus plug and endobronchial infiltration with eosinophils and peripheral eosinophilia in our case suggest a possible hypersensitivity damage to airways leading to dilatation and mucus impaction. This entity is not related to asthma, ABPA or other known causes of mucoid impaction. It has favorable response to steroid.[16]

Acute mortality has been reported with mucoid impaction secondary to asphyxiation, but long-term prognosis has not been reported. A long-term inhaled steroid use is recommended in some case reports with significant response in cellular or inflammatory casts,[16] while no response has been described in a cellular cast. To our knowledge, this is the first case report of mucoid impaction with significant response to short-term use of oral steroid with complete resolution of clinical symptoms and radiological findings (Figure 3). The patient remained asymptomatic without inhaled or oral steroid maintenance therapy, with reduction in the airway dilatation suggesting reversible airway damage or dilatation.

We recommend that after a careful exclusion of the secondary causes, initial diagnostic bronchoscopy, broncho-alveolar lavage, and establishing the diagnosis of cellular casts, a short course of oral steroids with or without maintenance inhaled steroid therapy be used. A long-term clinical follow-up along with serial chest x-ray of possible cases is needed to establish the effectiveness of treatment and long-term prognosis.

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A RARE SEQUENTIAL OCCURRENCE OF CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING CHRONIC MYELOID LEUKEMIA

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The association of chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) in the same patient is very rare. There are a few reports in the literature of such cases, the majority of which correspond to CML occurring during the evolutive course of CLL. We report a patient who developed CLL 18 months after he was diagnosed to be suffering from CML. There is only one other report of such a sequence occurring in the same patient. The case is discussed with reference to the literature.

Case Report

A 57-year-old man presented to our institution with an abdominal mass. He had splenomegaly of 15 cm. His total WBC count was 72x10^9/L, with a differential count of blasts 1%, promyelocytes 2%, myelocytes 9%, metamyelocytes 5%, band forms 4%, polymorphs 64%, lymphocytes 4%, eosinophils 3%, and basophils 6%. His hematocrit was 46% and platelet count was 560x10^9/L. The leukocyte alkaline phosphatase score was 12 (N 85-95). Bone marrow aspiration and biopsy showed myeloid and megakaryocytic hyperplasia. Cytogenetic analysis of the bone marrow revealed 46,XY,t(9;22)(q34;q11), the Philadelphia (Ph) chromosome being observed in all the 25 metaphases. A diagnosis of CML in chronic phase was made, and therapy with hydroxyurea was instituted. His counts gradually fell, and was maintained between 13 to 15x10^9/L.

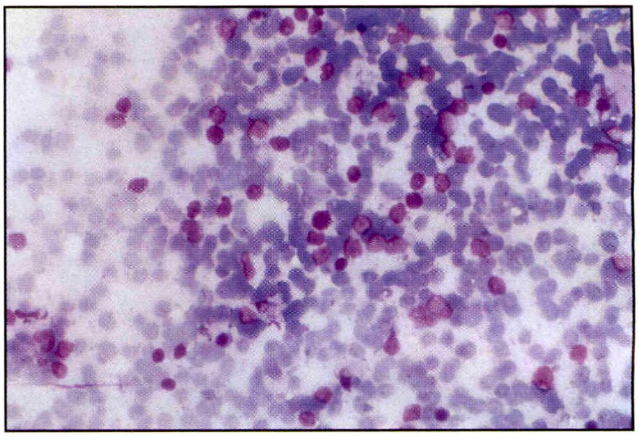

FIGURE 1A. Bone marrow aspirate smear showing sheets of mature lymphocytes (Wright's stain at 400x).

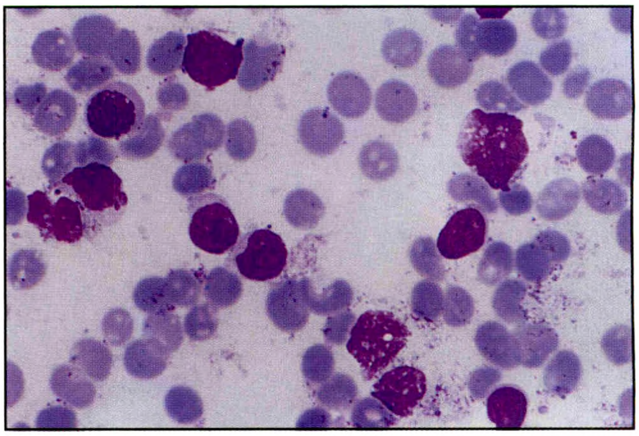

FIGURE 1B. Wright's stain at 1000x.

Eighteen months after the initial diagnosis, there was an increase in counts to 24x10^9/L, with a significant lymphocytosis. Bone marrow aspiration was done at this juncture. The smears showed sheets of lymphocytes, whose morphology appeared to be mature (Figure 1a & 1b). Immunophenotyping by flow cytometry was consistent with a diagnosis of CLL (CD5+, Cd19+, CD20+, CD 23+, Tdt-). Cytogenetic analysis of the bone marrow showed a persistence of the Ph chromosome and the presence of an additional anomaly: isochromosome (17)(q10) in 25% of the metaphases. The karyotype was interpreted as 6,XY,t(9;22)(q34;q11)[24]/46,XY,t(9;22)(q34;q11),i(17)(q10)[8]. The patient has been under observation for the past three months, and peripheral smears done at fortnightly intervals show significant lymphocytosis, with an occasional myelocyte, metamyelocyte and basophil.

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Discussion

The co-existence of CLL and CML in the same patient is rare. Most of the cases showing this association correspond to CML developing during the course of CLL. Esteve et al.[1] reviewed 13 such cases, and Mossafa et al.[2] have also reported another case. The time interval between the diagnosis of these cases varied from simultaneous occurrence to 87 months. The patients received various forms of treatment, such as chlorambucil, prednisolone with vincristine and bleomycin, or total body irradiation.

The second leukemia in these cases has been attributed to the carcinogenic effects of irradiation, or chlorambucil. The impaired immune surveillance in CLL may also have contributed to the development of the second leukemia. Esteve et al has reported a patient who developed CLL during the course of CML. The original bone biopsy, however, showed the presence of lymphoid nodules. The patient progressed to, and died, of a lymphoid blast crisis.

Our patient developed CLL 18 months after the diagnosis of CML. The bone marrow aspirate showed the presence of CLL, both morphologically, and immunophenotypically. The coexistence of CML was shown by the persistence of the Ph chromosome. An additional anomaly in the form of isochromosome 17(q10) was seen. This is seen as an additional abnormality in chronic myeloid disorders, and is associated with rapid progression to acute non-lymphocytic leukemia. Kantarjian et al.[3] studied 242 cases of CML in blast crisis, and found that isochromosome 17 (q10) signifies clonal evolution with a short survival. The bone marrow biopsy of our patient done 18 months after the initial diagnosis of CML showed evidence of both leukemias, CLL being evident in the smears and by immunophenotyping, and CML in the form of persistence of the Ph chromosome with an additional anomaly known to be associated with chronic myeloid disorders. The peripheral smears of the patient also reflected the dual leukemia, showing both a lymphocytosis, a shift to the left and basophilia.

When cases in which CML and CLL co-exist are encountered, a stem cell origin of both leukemias is an attractive hypothesis. The stem cell should be capable of differentiating along both lymphoid and myeloid lines. This hypothesis is particularly relevant in those cases in which both leukemias occur simultaneously. An attempt has been made to address this issue by means of molecular studies.

Esteve et al.[1] have used bcr/abl as a marker for the myeloid cells, and monoclonal rearrangement of the immuno-globulin heavy chain as a marker for the B-lymphocytes. Zollino et al.[4] and Maher et al.[5] have performed similar studies, and have been able to demonstrate two different and distinct cell populations. The CLL could, of course, be a chance occurrence in a patient already diagnosed to have CML. CLL does not have any known etiological factors, and is not associated with ionizing radiation, exposure to drugs or chemicals, and is the only leukemia not observed in survivors of atomic bomb explosions.[6]

Awareness of this rare sequence will be of use to a morphologist and clinician who would otherwise be perplexed by the appearance of a large number of lymphocytes in a patient being treated for CML.

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CONGENITAL ANTRAL MEMBRANE: CASE REPORT

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Mazen Kurdi, MS; Mansour Kilani, MS

Congenital antral membrane is a rare cause of gastric outlet obstruction in the newborn.[1] The symptoms attributed to this condition mimic those of pyloric stenosis. Treatment alternatives are incision and excision of the membrane, pyloroplasty, endoscopic dilation, or resection.

Case Report

A 3-day-old female baby was referred to our unit with a history of progressive, projectile non-bilious vomiting since birth. Vomiting was copious and occurred 30 minutes after every feed. The baby was born at full term by spontaneous vaginal delivery, with history of maternal polyhydramnios and abdominal mass in the fetal ultrasound at mid-trimester. The baby weighed 3 kg and was mildly dehydrated with hyperchloremic alkalosis. There was epigastric fullness but no mass felt on palpation. There were no other anomalies except for a small ventricular septal defect (VSD). Plain abdominal x-ray showed dilated single stomach shadow with fluid level. Gastrografin showed complete obstruction at the prepyloric region with a bulge suggestive of prepyloric membrane (Figure 1).

The baby was transferred to the neonatal ICU, where the fluid and electrolytes were corrected and the baby was stabilized for operation. At the operation, the stomach was dilated, gastrotomy was performed, and the nasogastric tube introduced to pass through the duodenum. A small pylorotomy was performed to ease the passage of the tube. A complete thickened diaphragm was seen without any identifiable opening. Excision of the membrane and pyloroplasty were performed.

The baby was started feeding on the 5th day with 5% dextrose and water every 3 hours but was not tolerating it well. On the 11th day, gastrografin study was done which showed unacceptable delayed passage of the dye (Figure 2).

A second laparatomy was performed which showed that fluid was not passing freely from the stomach to the duodenum. The pylorus was re-opened and complete excision of the membrane was done. Postoperatively, the baby was started on TPN for two weeks and recovery was uneventful. Follow-up gastrografin study showed free flow of the dye all through the gastrointestinal tract (GIT) Normal feeding was then started, and the baby was discharged home after a week.

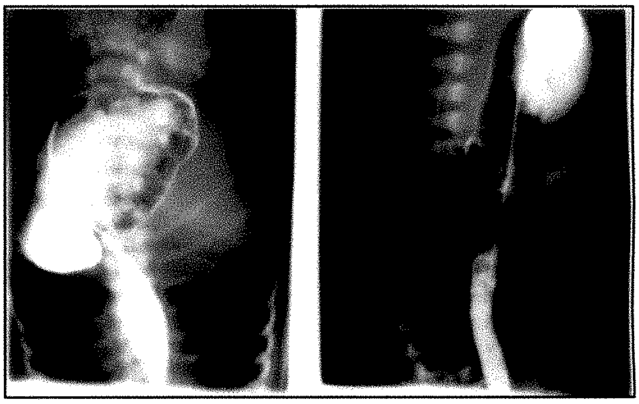

FIGURE 1. Gastrografin showed obstruction at the prepyloric region.

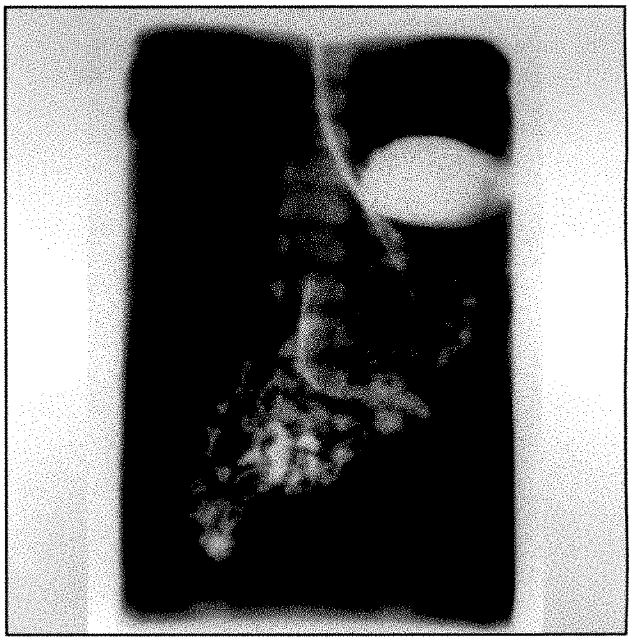

FIGURE 2. Follow-up gastrografin study showed unacceptable delayed passage of the dye.

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Discussion

Antral membranes (web or diaphragm), usually located within 1-3 cm proximal to the pyloroduodenal junction are thin, soft and pliable.[1] They are composed of mucosa and submucosa with an orifice (2 to 3 mm) of sufficient strength to resist manual dilatation.[2,3] Previously, these membranes were believed to arise from failure of recanalization of the embryonic foregut.[4] This has been challenged because the Tandler proliferative phase is not seen in the stomach. Thus, the membrane probably represents the developmental products of excess local endodermal proliferation and redundancy.[5]

Establishing the diagnosis of antral membranes can be difficult. The medical history of the patient, contrast roentgenologic studies, and endoscopic findings should all be taken into account. Other conditions that can mimic the case are pyloric stenosis, gastric web, pyloric atresia, ectopic pancreatic tissue, duplication of antrum and pylorus, gastric mucosa prolapse, gastroduodenal intussusception and congenital microgastria. In our case, the diagnosis was obvious by the clinical presentation and radiological studies, i.e., plain x-ray and contrast study. A combination of maternal polyhydramnios and fetal gastric dilatation indicated proximal gastrointestinal obstruction.[6] In case of duodenal obstruction, one should expect a duodenal dilatation along with the stomach (double bubble), but in our case, there was no double bubble shadow on plain x-ray. In a series of 29 cases of proximal gastrointestinal obstruction by Bronsther et al., 16 had history of maternal polyhyramnios.[7]

Pyloric stenosis can easily be excluded by the age of onset of the symptom, ultrasound findings and contrast studies. In our case, there was a very small hole in the membrane which was not seen through gastrostomy or negotiated by the nasogastric tube. As the apex of the bulged membrane was not accessible through the stomach, we had to do the pylorotomy in the first operation. The re-adhesion occurred probably due to incomplete excision of the membrane.

The management of antral membranes is either surgical or non-surgical. In surgical treatment, excision of the membrane and Heineke-Mikulicz pyloroplasty is curative.[8] It is most effective in symptomatic patients. Endoscopic transection or balloon dilatation may be an easier alternative in non-obstructive membrane sometimes found incidentally, or it can be managed conservatively.

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MICROGEL ELECTROPHORESIS (COMET TEST) FOR DETECTING DNA DAMAGES IN ORAL CONTRACEPTIVE USERS

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Hormonal drugs occupy a very important place in the chemotherapeutic treatment of various metabolic, homeostatic and sexual disorders.[1] Estrogens also fall under this category, and are extensively used for the treatment of many types of sexual disorders in both sexes. Ethinyl estradiol is a natural steroidal estrogen and is used as replacement therapy in women with abnormally low levels of estrogens. It is also used as a primary form of contraceptive in a combination of progestins.[2] These contraceptive hormonal drugs can influence the estrious cycle, mating and fertility in mammals. Their actions take place through inhibiting the secretion of pituitary gonadotropins and subsequent intervention with estrious cycle, ovulation and estrogen secretion.[1]

Direct evidence for the implication of contraceptive hormonal drugs at the genetic level comes from cytogenetic studies. During the last few years, several reports have appeared which showed types of structural DNA damages in different types of living organisms.[2] In this study, microgel electrophoresis (comet test) was used for detecting DNA damage. The comet test (comet assay), using a single-cell gel electrophoresis method was first reported in 1984 by Östling and Johanson to detect DNA double-strand breaks under neutral conditions.[3] Subsequently, Singh et al. introduced an alkaline version of this assay for detecting single-strand breaks produced directly or via alkaline-labile sites.[4]

Materials and Methods

This one-year study was performed on 57 women who presented to our gynecology unit for nonspecific complaints between 1998 and 1999. Thirty-three women had used combined oral contraceptive drugs as a birth control method, while 24 had not used any. All 33 patients had been taking oral contraceptive preparation which contained ethinyl estradiol and desogestrel for five years.

Culture Method for Comet Assay

The patients' blood was collected in heparin during their menstrual periods. 0.5 mL of whole blood was added to 5 mL RPMI-1640 medium containing fetal calf serum (FCS), phytohemagglutinin, antibiotics and L-glutamine under aseptic conditions. Bromodeoxyuridine was added at zero hour. The cultures were incubated at 37°C for 72 hours in the dark. At the 70th hour, 0.1 mL colcemide was added. At the end of 72 hours, the cultures were centrifuged at 1000 rpm for 10 min. The supernatant was discarded and 5 mL of 0.56% potassium chloride was added during mixing by vortex. It was left for 30 min at 37°C following the second centrifugation step for 10 min at 1000 rpm. The supernatant was discarded and the pellet was mixed with freshly prepared cold fixative (1:3, acetic acid: methanol). The cell suspension was left overnight at –20°C. The next day, the fixative was changed twice and the cell suspension was spread on slides which were pre-washed by alcohol and distilled water. After leaving the slides for one day, they were stained by Hoechst-Giemsa method.

Comet Assay

The comet assay, as described by Singh et al., was used with some modifications. The comet assay protocol was carried out under dim light to prevent any additional DNA damage. Darkened fully frosted microscope slides were each covered with 100 µl of 0.5% normal melting point agarose in calcium and magnesium-free PBS at 45°C. They were immediately covered with a large No. 1 cover slip and then kept at 4°C until the agarose had solidified. Seventy-five µl of 0.5% low melting point agarose (LMA) at 37°C was added to the lymphocytes (1500-100,000 cells), suspended in 10 µl of PBS. After gently removing the cover slip, the cell suspension was rapidly pipetted on to the first agarose layer spread using a cover slip, and allowed to solidify at 4°C. A final layer of 75 mL of 0.5% LMA was applied in the same way. The slides were immersed in freshly prepared, cold lysine solution for 1 hr at 4°C. Slides

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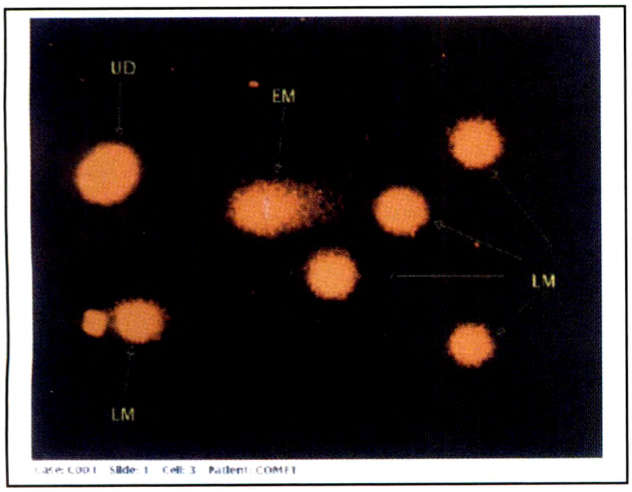

FIGURE 1. A photograph of cell damages by Comet assay.

TABLE 1. *Comparing the comet scores and ages of the control and study groups.*

	Control group Mean±SD (n=24)	Study group Mean±SD (n=33)	*P*-value
Age	32.2±5.8	30.9±4.7	>0.05
No migration	95±2.7	93.3±3.0	<0.05
Little migration	3.3±1.8	4.8±2.3	<0.01
Extent migration	1.8±1.7	1.8±1.5	>0.05

were removed from the lysine solution, drained and placed in a horizontal gel electrophoresis tank side by side with the agarose end facing the anode. The slides were left in the alkaline buffer (pH 13) for 20 min to allow unwinding of the DNA to occur before electrophoresis. Slides were then drained, placed on a tray and flooded slowly with three changes of neutralization buffer (0.4 M Tris, pH 7.5) for 5 min each, to remove alkali and detergents. The slides were again drained before being stained with 50 µl of 20 µg/mL ethidium bromide and a cover slip placed on top. Slides were stored in a closed container at 4°C and analyzed within 24 h, as gel dehydration over longer storage times lead to detoriation in slide quality.

Comet Scoring

Analysis was performed immediately after staining, using a 200x lens with a Nikon microscope equipped with an excitation filter of 515-560 nm from a 100W mercury lamp and a barrier filter of 590 nm. Comets from broken ends of the negatively charged DNA molecule become free to migrate in the electric field towards the anode. The assay provides direct determination of the extent of DNA damage in individual cells. The extent of the damage can be assessed from the length of DNA migration which is derived by subtracting the diameter of the nucleus from the total length of the image. The tail length can also be measured from the trailing edge of the nucleus to the leading edge of the tail, using a calibrated scale in the ocular of the microscope. The simplest method for collecting comet data is by determining the proportion of cells with altered migration. However, this approach is generally limited to electrophoretic conditions where the majority of control cells exhibit little or no migration of damaged cells.

A minimum of 100 cells were analyzed for each sample population. Slides were scored blind by two independent investigators, and cells were graded as to the extent of migration. Statistical comparisons between the grade of DNA damages in control/patient groups were analyzed by using Mann-Whitney *U*-test. Student's *t* test was used to verify that the two groups of women in this study were properly matched for age.

Results

The mean age of the patients was 31.4 years (range 22-43). All were multiparous and had more than two children. None had any systemic diseases. Smokers were excluded from the study. Table 1 shows the comet scores and ages of patients and controls. As shown, the ages were similar in the two groups ($P>0.05$). We found significant statistical differences between the study and control groups according to the criteria of the group which had no migration and little migration ($P<0.05$) The camera attached to the microscope by special adapter obtains an image of the fluorescing cells. In the photograph all the types of cell damages that we obtained by comet assay are as shown (Figure 1).

Discussion

A major breakthrough in the problem of human population control was achieved by the introduction of synthetic steroids as contraceptive drugs. A large sector of the female population is now dependent on the pills as an efficient means of birth control.[5] Unfortunately, there has been no consensus on the real effect of the steroid drugs from a genetic aspect. Earlier work conducted by Badr and Badr had demonstrated a high incidence of dominant lethal mutations in female mice given a large dose of these drugs.[6] On the contrary, Wallace et al. found lyndiol (lymstranol and mestranol) not to affect the frequency of dominant lethal mutations in mice,[7] and Dutokowski et al. reported no genotoxic effects for mestranol and norethindrone on micronuclei formation.[8] Liehr et al. reported that estrogens induced the formation of endogenous DNA adducts both in human and animals, and could ultimately lead to cancer development.[9,10]

Another study in 1993 by Wolff reported that cyproterone acetate, as a contraceptive steroid, may also have a tumor-initiating potential in rat liver, in addition to its tumor-promoting activity.[11] Also, Sarihyan observed that estrogens, namely ethinyl estradiol and mestranol treatment in mice *in vivo* enhanced the number of sister chromatid exchange cell in bone marrow cells.[12] This result was similar to Wolff's. The dose-related significant increase in the frequency of micronuclei and sister chromatid exchanges in the erythrocyte cell population of mouse bone marrow at all concentrations of the drug indicated its clastogenic potential.[11,12] However, other series failed to find any significant increase in numerical or structural DNA damages in women who had used the pill.[13,14] Many other studies have also reported hormonal drugs to be either mutagenic or nonmutagenic.[15] Perhaps this is due to the use of different *in vitro* and *in vivo* assay systems, namely, Ames test, mouse bone marrow studies and host-mediated assay using *Salmonella typhimurium* as indicator organism.[16,17] Another reason may be the different dosages of the drugs. In fact, most steroids are target cell specific for their physiological activities and influence the functioning of the target eukaryotic cells through a specific mechanism of action which may not be operative in prokaryotic cells, as well as in the non-target eukaryotic cells.

In this study, it is seen that oral contraceptives mostly caused DNA damages at low damage levels. The study group had used low dosages of oral contraceptive drugs. We used the comet assay, which has been accepted as sensitivity and rapid method for DNA strand break detection in individual cells since 1984. This assay has become widely applicable in industrial, environmental and genetic toxicology.

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TRANSNASAL ENDOSCOPIC SURGERY FOR RESECTION OF ANGIOFIBROMA WITH AND WITHOUT ARTERIAL EMBOLIZATION

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Juvenile nasopharyngeal angiofibroma (JNA) is a benign vascular tumor arising in the posterolateral wall of the nasal cavity at the superior margin of the sphenopalatine foramen.[1] This is an aggressively expansile lesion that occurs exclusively in prepubescent or pubescent males. Its incidence is approximately 0.05%-0.5% of head and neck tumors.[2] Pathologically, JNA is composed of vascular spaces within a fibrous stroma without any intervening smooth muscle between them, which contributes to the capacity for massive bleeding.[3] The vascular supply is usually derived from branches of the external carotid artery, although branches from the internal carotid artery may contribute.

As JNA expands, it initially extends anteriorly into the nasal cavity, superiorly into the sphenoid sinus, and laterally through the sphenopalatine foramen into the pterygomaxillary fissure. From the pterygomaxillary fissure, the tumor may spread into the infratemporal fossa, into the orbit through the inferior orbital fissure, or into the middle cranial fossa through either the foramen lacerum or superior orbital fissure.

Intracranial extension may also be a result of erosion through the sphenoid sinus.[4] The most frequent presentations of JNA are epistaxis and nasal obstruction which occur in more than 80% of patients.[5] Diagnosis is based on a thorough history, physical examination and radiographic findings that are so compelling that biopsy is seldom required before treatment.[6] Treatment options primarily include surgery and radiation therapy. Because of the long-term sequelae, radiation as primary management is of much concern.[7] The variety of surgical approaches to this tumor has increased with technological advances in imaging and embolization. With the prevalent use of endoscopes, a growing literature exists on the endoscopic treatment of JNA.[4,8,9] This article reports an experience in managing JNA patients via a transnasal endoscopic approach with and without embolization.

Patients and Methods

Between March 1997 and June 2000, we operated on 16 patients with JNA at the Amir Alam Hospital in Tehran, and the Rahnemoon Hospital in Yazd, Iran. All patients were male and ranged in age from 9 to 27 years (mean 16.5 years). All the cases were investigated with CT and/or MRI and carotid angiography, and the tumors were staged according to the classification system of Session et al.[10]

Of the 16 cases, 14 were being operated on for the first time for the condition, while two were for recurrence. Once total removal had been achieved, CT or MRI was used, in addition to periodic endoscopy for follow-up, usually initially at six-month intervals. The technique is dependent on location and extension of the tumor. Preoperative endovascular tumor embolization was used in all, except three cases before surgery. All cases were operated under general anesthesia with controlled hypotension, with adrenalin-soaked gauze placed in the nasal cavity before surgery for better vasoconstriction.

After gauze removal, the tumor is slowly pulled down with application of a retractor to expose the sphenopalatine foramen, which is the origin of the tumor. Then the tumor is carefully pulled out of foramen, usually with a seeker. If there is extension to the lower part of the pterygomaxillary fossa or to the infratemporal fossa, the inferior part of the inferior turbinate is reseated or pushed inferoposteriorly. This manuver exposes the superior, inferior, medial and lateral aspects of the tumor. The tumor is then grasped and pushed medially to expose its origin. After removal of the posterior wall of the maxillary sinus and elevation of the retromaxillary periosteum, the infratemporal fossa is made accessible. Then the tumor and surrounding soft tissues are pushed inferomedially and the pterygopalatine fossa is cleaned. After this, the tumor is pulled out from the nostril, or in larger tumors, from the mouth. It is an important point to ensure that the tumor is not cut into pieces but pulled en bloc. Cutting a tumor into pieces results in massive bleeding and allows the intraforaminal portion to get back into the foramen. After the surgery, the nasal cavity is

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packed for two days only in patients without embolization. All patients are ready for discharge after two days of hospital stay.

Results

All the 16 patients had CT scan before definitive treatment. All cases were Stage I (A or B) or Stage II (A or B). In three patients, the operation was done without immobilization.

In all patients, follow-up CT scan was performed after six months postoperatively. Follow-up time was between 18 and 57 months, (mean of 44.1 months). During the follow-up period, no case of recurrence or major complication was seen.

Discussion

The treatment of JNA is a challenging issue. In our 16 patients, endoscopic surgery was the only means of treatment. Although selection of better treatment techniques should be based on controlled prospective trials considering the spectrum of JNA, it may be possible to make a better choice. Although endoscopic surgery has been used in recent years for treatment of JNA,[4,11,12] due to the limited number of patients, there is as yet no definite conclusion as to its suitability.

Intraoperative bleeding is a major issue for endoscopic surgery of JNA, but preoperative embolization, multiple intraoperative packing, controlled hypotension and application of local vasoconstriction can limit it. In none of our patients did uncontrollable bleeding occur, and only four received transfusion.

Another limiting factor for endoscopic surgery is tumor location/extension, although this is a limiting factor for external approaches, as well.[13]

Endoscope surgery has no major morbidity, no scars, no injuries to nerves and vasculature, and no facial developmental problems. In addition, the length of postoperative hospital stay is significantly shorter than open approaches. In our series, the mean length of hospital staying was two days.

Recurrence of tumor is a major problem after surgical excision of JNA (endoscopic or open). Factors influencing recurrence include stage of tumor and its location.[14] In addition, there is a report of increased recurrence rate after embolization.[15] Because of small tumor size and good visualization of tumor extension, there is small rate of tumor recurrence after endoscopic surgery.[6] Jerrisen et al.[14] in a review of some previous studies reported no recurrence after endoscopic approach. In our study, no case of recurrent disease was seen.

Indications of endoscopic surgery for JNA are not yet generally agreed upon. The controversy is not about using endoscopic surgery but the stage in which it could be used. It seems that early stages of JNA (IA, IB, IIA) are more suitable for this approach.[12]

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BLUNT TRAUMATIC DIAPHRAGMATIC RUPTURE IN CHILDREN

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Traumatic diaphragmatic rupture is a relatively rare entity, with only a few reported pediatric cases. Specific differences from adult traumatic diaphragmatic rupture are found more in the cause and frequency than in diagnosis and treatment of this disease. We present these four cases of traumatic diaphragmatic rupture, which were managed in our department for a six-year period from January 1994 to December 1999.

Case Reports

The charts and radiographs of pediatric patients who had sustained blunt trauma with rupture of the diaphragm were retrospectively reviewed. All patients were admitted to the emergency room (ER) where they were assessed and imaging studies performed. The follow-up on these patients was more than six months.

Case 1

A 10-year-old boy was struck by a car, and sustained head, chest and abdominal injuries. He was intubated at the scene of the accident and presented to the ER one hour later with shallow respirations, hypotension and unconsciousness. Investigations on admission included chest x-ray, abdominal ultrasound and CT scan. The chest x-ray showed an opaque right hemi-thorax and the ultrasound and CT scan confirmed the displacement of the right hepatic lobe into the thorax (Figure 1). The patient was initially stabilized and an intravenous cholangiogram was performed to rule out an associated biliary duct injury, which was intact. At laparotomy two hours after admission, the right hepatic lobe was reduced and a large right diaphragmatic laceration with peripheral disruption repaired. No other injuries of the liver were identified. The postoperative course was uneventful.

Case 2

An eight-year-old boy was struck by a motor vehicle and admitted to the ER, with complaints of abdominal pain, nausea and dyspnea. A chest and abdominal x-ray with barium confirmed a left diaphragmatic rupture by the presence of a bowel pattern in the chest, and a naso-gastric

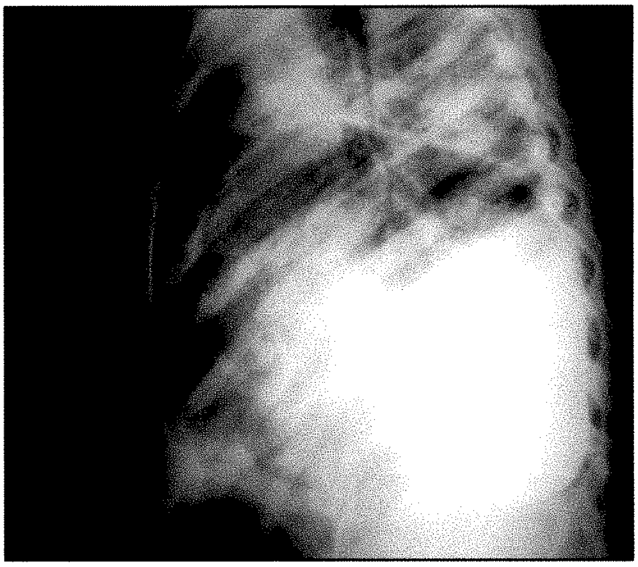

FIGURE 1. Right liver lobe and gallbladder seen in the right hemithorax.

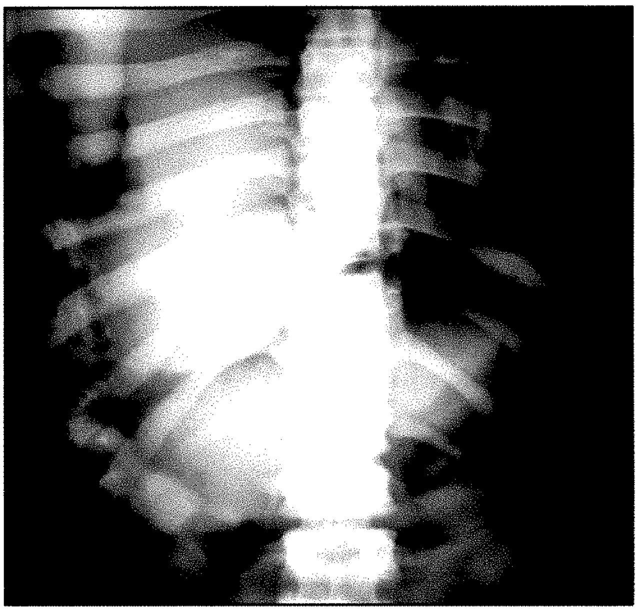

Figure 2. Diaphragmatic rupture simulating diaphragmatic eventration.

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tube curling up into the chest. At laparotomy, a left diaphragmatic rupture was found. The stomach and transverse colon were reduced from the thorax, and the transverse centro-lateral diaphragmatic rupture was repaired. The postoperative course was uneventful.

Case 3

A four-year-old girl was admitted to ER with a history of having been crushed by a heavy beam from a swing set which fell on her epigastrium causing skin abrasion. Her respiratory status rapidly deteriorated in the ER (about 30 minutes after the trauma), and she required intubation and right chest tube insertion for pneumothorax. Radiological studies including chest and abdominal x-rays and CT scan did not confirm a diaphragmatic lesion, but they did reveal contusion to the base of both lungs, a right pneumothorax, pneumomediastinum and a retropneumoperitoneum. A repeat chest x-ray two hours later showed a rupture to the left hemi-diaphragm, by the presence of a bowel pattern in the chest. The rupture was confirmed with an UGI barium study, and the patient taken to the operating room. At surgery, a linear ruptured diaphragm was found which involved only the central fibrotic portion and extending laterally on the left side. There was herniation of the stomach and transverse colon into the chest. The rupture was repaired and the child was discharged after two weeks.

Case 4

A three-year-old girl presented to the ER with a history of being crushed between a 4-wheel drive vehicle and a garage wall. She was admitted one hour after the trauma in stable condition but she had grunting respiration, tachycardia and unexplainable hypertension (200/100). Chest and abdominal x-rays showed a convex left hemi-diaphragm pattern and suggestions of a contusion to the lower lobe of the left lung. A comparison with previous films ruled out a previous diaphragmatic abnormality. The suspicion of diaphragmatic rupture was entertained due to continued clinical deterioration and deformity of the stomach with abnormal location, for which surgery was undertaken (Figure 2). At surgery, we found a complete laceration of the central fibrotic portion of the left hemi-diaphragm which extended into the inferior and lateral aspect of the pericardium. When the stomach, spleen and transverse colon were reduced from the thorax, we found that the heart had been dislocated out of the pericardium into the left chest. The pericardium was partially repaired to prevent a constriction, a chest tube inserted and the diaphragm sutured.

Postoperatively, the patient's respiratory and circulatory status was restored. After surgery, abdominal drain began draining about 300 cc. of yellowish fluid (chyle) per day from her abdomen for three weeks, developing into peritonitis. This chylous drainage decreased progressively only to resolve spontaneously after 6 weeks without specific treatment. The chyle was of unknown origin, as the diaphragmatic rupture was not extended back to the crura.

Discussion

Blunt rupture of the diaphragm is uncommon, occurring in approximately 3% of patients with abdomino-thoracic trauma.[1-2] When present, it suggests the presence of severe trauma. Described first by Semertus in 1541, Rialfi performed the first successful repair in 1886, and it was not until 1951, when Carter et al. published the first case series, that this injury was well understood and delineated.[3] In adults, motor vehicle accidents are the most common cause 71%,[4] and males are predominantly affected (male:female = 4:1).[5-6] Little data is available on diaphragmatic rupture in children. In our review, motor vehicle crash-related accidents were the major cause of this abdomino-thoracic trauma in 3 out of the 4 cases.

Diaphragmatic rupture can be cupular, sagittal, paravertebral, retropericardial or frontal transverse with peripheral disruption. Frontal transverse ruptures are always seen on the right side. Greater than 60% of diaphragmatic ruptures are on the left side, while less than 5% are bilateral.[6-8] Pericardio-diaphragmatic ruptures are very rare.[9,10]

Diagnosis remains difficult because diaphragmatic rupture is often associated with other visceral injuries that may mask the clinical or radiological signs. Splenic rupture or liver laceration is present in 25% of blunt traumatic diaphragmatic rupture,[11-13] however, aortic tear has as yet not been reported in children. In 10%-50%, diagnoses are not made in the first 24 hours. Diaphragmatic injuries are often overlooked, and there is no gold standard for early detection and reliable diagnosis. Early diagnosis is based on a high index of clinical suspicion and may require repeated radiological studies. Chest radiographs, including anterior-posterior and lateral views, in the erect or sitting position are the initial imaging modality to screen the patient,[14-16] UGI barium studies are helpful in making the diagnosis in complicated patients.

Ultrasonography and CT examination is becoming the standard method of evaluating patients with blunt abdominal trauma. These investigations may reveal diaphragmatic thickening (seen with diaphragmatic rupture), which is a useful diagnostic sign.[17] However, the specificity and sensitivity of these examinations are variable,[18-20] nevertheless CT scan is important because of associated visceral injuries.

MRI imaging and MRI angiography should not be considered as a primary study for the patient who has sustained blunt trauma .MRI imaging is a useful ancillary tool to confirm or to exclude diaphragmatic injury. Finally the role of thoracoscopy and laparoscopy both for diagnosis and therapy is important.[21-23] The appropriate approach is selected after taking into consideration other associated injuries. Once recognized, the approach to surgical repair is straightforward, with a simple layer repair using a heavy non-resorbable suture via a trans-abdominal approach. These complex injuries can test the surgeon's skill and creativity.[24-25]

Early deaths are usually a result of associated injuries. Paralyses or incordination of the diaphragm is common but over 50% of this condition resolve in two weeks. Late complication of an undiagnosed traumatic diaphragmatic hernia of the abdominal content, incarceration, strangulation or herniation into the pericardial sac and tamponade should be prevented by early diagnoses.[26-27]

In conclusion, blunt traumatic diaphragmatic rupture is a rare condition in children. Early diagnoses are based on a high index of clinical suspicion and repeated imaging studies. Prognoses usually are related to the associated injuries.

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A FIVE-YEAR EXPERIENCE OF A SHORT STAY OBSERVATION UNIT IN SAUDI ARABIA

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Many hospitals have Observation Wards (OWs) attached to their Emergency Rooms (ERs), whose utilization varies from one country to another. In the US, these Observation Wards have evolved mostly into Chest Pain Observation Units (CPOUs) for patients whose clinical features of chest pain are suspicious but not diagnostic, and of acute myocardial infarction patients who can be observed further before either being discharged home or admitted to hospital. In the UK and other countries, they are used for more variable purposes including trauma, psychiatric observation, geriatric assessment, pediatric emergencies and cases of drug overdose.[1-6]

Observation Wards have multiple functions, therefore, their cost impact on other medical services varies according to the circumstances of use. However, even for CPOUs with specific roles,[7] it has been more difficult to assess cost impact. CPOUs have been shown to be cost-effective in the US[8,9] and in the UK, hospital beds have been saved as a result.[1,10,11] This report describes the utilization of a short-stay observation unit (Stabilization Unit) in a Saudi Arabian health center, where the circumstances are unique.

Background

Saudi Aramco-Al-Hasa Health Center (SA-AHHC) is part of Saudi Aramco Medical Services Organization (SAMSO), which is responsible for providing health care services to eligible employees and dependents of the Saudi Arabian Oil Company, Saudi Aramco. It has a busy outpatient service where 400,000 patient visits are made annually, mostly to general medical practitioners, supported by specialist pediatricians, obstetricians, internists, radiologists and anesthetists. It has 80 beds for pediatrics, obstetrics and gynecology, as well as an emergency service, which is open 24 hours daily.

The Stabilization Unit (SU) is a 3-bed observation area attached to the Emergency Room, where patients can be kept for up to 36 hours. This time duration is utilized to separate such patients from inpatients who usually stay for 48 or more hours, in accordance with Joint Commission for International Accreditation (JCIA) standards. The SU opened in August 1993 under the supervision of the Internal Medicine Unit for utilization by the three main specialties—medicine, pediatrics and obstetrics/gynecology—enabling further care and observation of patients who require more than the 6-hour period allowed for patients in the ER. Division of available space into cubicles allowed flexibility in admission of patients of either gender. Nurses are assigned to the SU as needed, from the ER nursing staff to which they belong.

Medical patients requiring hospitalization are usually transferred to the Saudi Aramco-Dhahran Health Centre (SA-DHC), about 140 kilometers (90 minutes) distance from SA-AHHC by ambulance. The round trip takes approximately 5 hours, including handover and ambulance waiting time. Many of these patients require some initial treatment to stabilize their condition to make them fit and safe for their transfer to SA-DHC. The SU was expected to play an active role in this process, as well as in reducing both the numbers of short stay admissions to SA-DHC and transfers to local hospitals. The usage of the SU function was monitored and studied from September 1993 to September 1998, and compared with the experiences of similar units elsewhere. The findings are believed to have implications for other health care institutions in this era of greater awareness of healthcare delivery cost and efficiency.

Description of Service

Adult patients (aged 14 years and over) with significant internal medicine problems who presented to the emergency service of SA-AHHC were initially evaluated by ER physicians and referred to the Internal Medicine service, as necessary. About 3500 such referrals were made each year of which 40% needed further care. Most of these patients requiring further care were admitted directly to SA-DHC and the remainders were treated in the SU. Patients were admitted into the SU for one or more of the following reasons:

- initiation of stabilizing treatment requiring several hours, prior to transfer to SA-DHC
- self-limiting acute problems, e.g., dehydration from gastroenteritis

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TABLE 1. *Patient admission and disposal, 1993-1998.*

Year	No. of patients admitted	No. of patients discharged home	%
1993	116	103	87
1994	358	268	75
1995	453	372	82
1996	476	348	73
1997	497	397	80
1998	355	276	78
Total	2255	1764	Mean % 78.3

TABLE 2. *Top admissions to stabilization unit, 1993-1998.*

Year	1993	1994	1995	1996	1997	1998	Total
SCD	33	61	59	11	131	105	502
Infections	30	35	87	73	88	60	373
Cardiac	26	76	73	57	41	26	295
GIT	18	50	68	31	59	31	257
COPD	22	41	51	37	41	35	227
Asthma	14	40	39	34	39	29	195
DM	20	32	33	33	33	19	170
Totals	163	335	410	378	432	305	2019

SCD=sickle cell disease; GIT=gastrointestinal disorders; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus-related problems like hypo- and hyperglycemia.

TABLE 3. *Cost of health service items (1998).*

Item	Unit cost ($)	Cost for 1764 patients ($)
Ambulance (to DHC)	160.00	282,240.00
Nurse escort	200.00	352,800.00
Physician attendance	47.00/day	248,724.00
Inpatient service	276/day	1,460,592.00
Meals	122/day	430,416.00
Total		$2,774,772.00

Round trip AHHC-DHC takes approximately 5 hours; nurse escort cost is $40/hour; each short admission is estimated @3 days; meals are for 2 days, excluding the time spent in SU.

- expected short-term stay, e.g., control of painful sickle cell disease crisis
- initiation of parenteral antibiotic treatment in severe uncomplicated infections, e.g., pneumonia
- initiation of treatment in ambulatory patients too ill for routine outpatient treatment
- management of miscellaneous clinical problems, where intensive care or further special care and investigations available only at SA-DHC are not required.

Patients in the SU were reassessed frequently, approximately every 6 hours, to consider final disposition, with main decision being made between 18 and 36 hours after admission. Those making only slow progress, or whose problems became complicated, were transferred to the base hospital, SA-DHC. Transfers were made as soon as the need for them became obvious, and in any case, before the expiry of the maximum allowed time of 36 hours. Cost analysis is outlined in Table 1 at the company's rates available for 1998, assuming a mean short-stay period of 3 days per patient. This conservative estimate of length of stay offset the small inflationary element inherent in pricing the 5-year activities at 1998 prices.

Results

The extra clerical work and routine documentation involved in first discharging patients from the ER, and then admitting them to the SU for stabilization of their condition, before transfer to SA-DHC became obvious during the first year of operation. In subsequent years, therefore, those patients needing this type of care were generally treated in the ER before being transferred. Thus, the SU ended up being, in practice, a short-stay ward. Similarly, although pediatric and gynecological patients could be admitted into the SU, patients of these two services were mostly admitted to their respective wards, since these were available at SA-AHHC. Thus, nearly all SU patients (97.5%) were medical.

During the five years of this report, 1764 out of 2255 patients (78%) were discharged home from the SU. These patients would have been short-term admissions to the base hospital, if there were no SUs. The Health Center cost savings included those on ambulance trips, nurse escorts, hospitalization with daily physician attendance, and feeding.

Table 1 and 2 summarizes the results of patient categories and usage. Both sexes were equally represented with 51% males and 49% females. The mean age of patients was 48.5 (range 14-92) years. Ninety percent (90%) of all the medical admissions to the SU were accounted for by seven main diagnostic categories, while nearly three quarters of them (73%) were from the top five. Sickle cell disease (SCD) vaso-occlusive pain crisis was the most common single admission entity, with nearly one-quarter (22.3%) of all the admissions. These proportions did not vary much from year to year. About 80% of the patients were discharged home, with little year-to-year variation. Sickle cell disease again topped the list of those eventually transferred to hospital, making up about 30% of the total number.

Patients spent an average of 21.4 hours in the SU, with little difference between those discharged home (21.7 hours) and those transferred to hospital (20.5 hours). SCD patients stayed longer, but the pattern was the same, with mean stay period of 25.3 hours, and 25.2 hours, respectively. In some cases, the transfers occurred less than 12 hours after admission, indicating prompt clarification of the clinical problem. The use of the SU significantly reduced the number of patient transfers to other hospitals during the study period.

Discussion

The SU discharge rate of cases that would have been short-stay admissions to hospital was approximately 80%. This seems to be the pattern in the use of most OWs [1,7,12-15] including the elderly, among whom 71% were discharged home in one report.[1] This was a major saving for SAMSO, which ensured acute SA-DHC bed availability for more needy patients requiring all the expert support and services of a major hospital. The total saving of almost $3 million (SR11 million) over five years or $0.6 million (SR2.2 million) per year from such a small unit of 3 beds is substantial. If ambulance and nurse escort costs are excluded, the savings would still be significant at $2.14 million (SR 8 million). Treatment in the SU was also more convenient for our patients as it was nearer their homes, enabling friends and relatives to visit.

OWs vary greatly in capacity and usage. For example, in the UK, unit bed space varies from 6 to 20,[6] while one unit in Hong Kong has over 34 beds.[12] The SA-AHHC SU of three beds is at the lower end of capacity and it is currently being expanded to 6 beds. For the period of study, our SU was not used for trauma or surgical cases, but this is about to change. The main observation drawn from this comparison is that successful OWs are flexible in bed capacity and usage, and both factors usually operate in response to local need.

The success of the SU in saving hospital beds and reducing the number of short-stay admissions and transfers to non-SAMSO hospitals was in part responsible for SAMSO's decision to double the SU capacity to 6 beds and increase the scope of its usage to include observation of surgical patients by ER staff. Other authors found that not only did OWs save hospital beds, but they also led to more prompt medical attention and earlier discharge from hospital.[1,16,17,18]

The increased proportion (30%) of sickle cell disease patients transferred to hospital, compared with that admitted to the SU (22%), suggested that more than 36 hours was needed to control the pain of vaso-occlusive crisis of these patients, or that the Internal Medicine Service pain management approach needed review, or both. This prompted further examination, leading to the issue being subsequently addressed. Time in the SU was extended to 47 hours when the unit reopened, and the Internal Medicine Service pain management protocol for sickle cell disease crisis was revised.

The prominent contribution of SCD to the SU admissions is a local phenomenon due to the prevalence of the disorder in the area of practice. It provided the opportunity to study the disease that led to modifications in practice. The trend for SCD patients to use the ER for most of their medical care was noted, and led to the commencement of a special SCD clinic which encourages continuity of care for these patients. In this clinic, patients and their families receive health education and counseling on how to look after themselves. This has resulted in reduction of both ER visits by SCD patients and loss of school time for the younger ones. It is currently the subject of further study. This opportunity to gain experience in the management of a specific disorder is similar to that of an OW in Wales, UK, where nearly two-thirds of cases were found to be drug overdoses and minor head injuries.[19]

In summary, the SU:

- saved money and valuable hospital beds
- increased patient satisfaction by enabling patients to be treated nearer their homes
- gave the opportunity to study and gain experience in a specific disease entity
- highlighted the multiple roles such a unit could play in the current search for quality but cost-efficient healthcare

There could be roles for units like the SU in diabetic management (e.g., initiating insulin treatment), patient dehydration where diarrhoeal diseases are common, minor medical and surgical procedures, post-trauma observation, self poisoning and other self-limiting conditions.

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RAISING WOMEN'S REPRODUCTIVE HEALTH AWARENESS: A COMMUNITY-BASED INTERVENTION PROGRAM IN JORDAN

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Over the past 30 years, there has been a gradual shift in the way women's reproductive health issues are addressed by the international development community, as seen in maternal and child health programs, family planning efforts, and the Safe Motherhood initiative. As a continuation of this paradigm shift, ensuring women's reproductive health needs are met throughout the life cycle was named as one of the key priorities of the International Conference on Population and Development in 1994.[1] However, ensuring reproductive health care services and information are available does not necessarily ensure that women make use of these services. In order for reproductive health services to be utilized, women need to know when they are in need of, and how to use this care. Health awareness programs are one way of empowering women with this knowledge about their reproductive health and available health services.

The issue then arises as to where health awareness programs can most effectively occur in the local context. Primary health care relies on health awareness messages being passed between health workers at any level (from physicians to community health workers) to members of the community.[2] In a developing country like Jordan where most health care services are provided to women via maternal and child health (MCH) programs, there are a number of barriers to providers' carrying out health promotion with patients. The few studies that have been conducted on health promotion in health care settings in Jordan indicate that the providers' time, knowledge, and negative attitudes towards health promotion pose barriers to health information exchange between provider and patient.[3,4] In one local study, all nurses and midwives working in a Northern Governorate's primary health care and MCH centers were asked about their opinions regarding health promotion. Fifty percent of nurses and midwives participating in the study stated they do not have sufficient time to work on health promotion, despite that 78% of the respondents stated they were the most appropriate people to be involved in health promotion.[3] Just over 50% of midwives and nurses went on to respond that they felt that health education was "guilt-inducing" and boring, with slightly more respondents stating that societal and cultural values influence Jordanian lifestyles to the degree that health education by a health professional cannot change local practices.[3]

Previously, Al-Qutob and Mawajdeh[4] conducted a comprehensive survey in MCH facilities in a northern Jordanian city. The researchers found that although all 31 directors of the facilities stated that health education was an integral part of the MCH services they offered to women, 74% of the directors felt providers in their centers did not have enough training in health education. This lack of specific training was made apparent when more than half of the pregnant women receiving prenatal care from the centers stated they were dissatisfied with the quality of information given to them by physicians and midwives.[4]

Given that Jordan does not yet have a national-level communication strategy on women's reproductive health and that the level of appropriate training and knowledge among MCH health care providers in the public health facilities is relatively low, it is expected that the level of knowledge on other women's reproductive health issues is even less. The question therefore arises as to the ability of local health care practitioners to spend the time to competently raise the health awareness of women on reproductive health issues. One solution, as examined in the paper at hand, is to use local peer health educators in the community to raise the level of awareness on certain issues. This approach not only provides local community women with health-related information about their reproductive health, but also empowers them to become active participants rather than merely recipients of health care needs tailored specifically to them.

Aims

As part of a larger reproductive health intervention study, the researchers aimed at increasing and improving women's knowledge on matters of female reproductive

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health in a designated community using local women from the same community. A case-control study was conducted to assess if participants' knowledge of women's health issues were affected in the short-term as a result of the health awareness project.

Methods

The study was undertaken in the town of Ain Al-Basha, 25 kilometers northwest of the capital of Jordan, Amman, between June 1999 and March 2000. The town is a semi-urban, as well as semi-rural industrial area, with a population of around 25,000, the majority of whom are of low socioeconomic status. The community is served by a public comprehensive health care center (CHC) system that includes referral care for the surrounding towns and villages. The area has good educational facilities for boys and girls. There is also a very active network of women's committees in the town.

The Health Awareness Intervention Project

This paper describes the health awareness project, which was part of a larger Reproductive Health Intervention Study, (RHIS) conducted in 1997. A case-control study design was used in an attempt to measure the short-term impact of the health awareness intervention project on the participating women. Women aged 20-45 years attending the health awareness sessions, or those receiving the intervention (n=113), lived in the immediate area surrounding the CHC.

A group of women living in the study community who did not participate in the health awareness sessions acted as the control group (n=200). To reduce the potential bias in the women's answers, residential blocks that were not included in the RHIS and located further from the CHC were included as controls. Although these women lived a relatively greater distance from the CHC than the women who received the intervention, the research team did not expect this to introduce any weakness into the study design as the town is relatively small in size. Study subjects were identified by randomly selecting homes from information on housing units provided by the Department of Statistics. The currently or previously married female head of household was asked to consent to participate from the selected houses. If her participation was not possible for any reason, the proceeding house was selected. Ten women from the six residential blocks refused to participate in the study.

The Message

The scope of the health education message used among women in the study community was based on several sources. The first source was the results of the RHIS as described above. The second valuable source of information came from a census conducted on women attending the MCH and Family Planning (FP) services at the local CHC, showing that few women attend the CHC for health services outside of MCH and FP services. Finally, observations by members of the study team of patient-provider interactions in the MCH clinic of the local CHC were the other source of information.

By using these sources of information gathered from the community, the health awareness units were developed. Ten health education units were developed, largely following the sequence of the woman's life cycle and major events within each phase. The 10 units were as follows:

- Comprehensive health as a human right and responsibility
- environmental health at home and in the community
- the impact of social perceptions on women's health
- comprehensive health care for girls during childhood and adolescence
- comprehensive health care during marriage and family life, including family planning
- fertility, conception and miscarriage
- pregnancy and delivery
- the first year with a baby
- women's health in her reproductive years
- dealing with menopause

Within each health unit, there were 5-10 main messages to be introduced to the women attending the sessions. Pre-testing was conducted in the community among five groups of women in focus groups ranging in age from 20 to 45 years. Changes were made to the messages by the research team based on the feedback from the focus group discussions.

Approach to Health Promotion

Female peer health educators were chosen from the community, because the project was concerned with raising health awareness in the community as a whole, and not only among women attending MCH and FP services. Selection of the health educators was based upon the person's communication skills and her level of activity in the community. The 11 women who were selected agreed to act as health educators, and underwent extensive training covering the content of the reproductive health messages and in communication skills.

Each educator was expected to introduce and discuss the 10 health education units to 10 currently or previously married women 20 years or older, living in the area surrounding the CHC. However, 10 single women did participate in the sessions, with permission from their families. The health education sessions took place in the home of the health educators. One member of the research team attended the weekly gatherings in the homes to ensure the messages were standardized and that the correct information was passed on to the women.

TABLE 1. *Frequency distribution of socio-economic characteristics for cases and controls.*

Characteristics	Cases n (%)	Controls n (%)
Age*		
19-29	38 (33.6%)	45 (22.5%)
30-39	51 (45.1%)	59 (29.5%)
40-49	14 (12.4%)	50 (25.0%)
50-75	10 (8.8%)	46 (23.0%)
Marital status**		
Single	10 (8.8%)	0 (0.0%)
Married	102 (90.3%)	191 (95.5)
Divorced	0 (0.0%)	2 (1.0%)
Widowed	1 (0.9%)	7 (3.5%)
Level of education		
No formal education	11 (9.7%)	39 (19.5%)
Primary, secondary	46 (40.7%)	69 (34.5%)
Tawjihi (high school degree)	28 (24.8%)	58 (29.0%)
College, university	28 (24.8%)	34 (17.0%)
Working outside the home		
Yes	10 (8.8%)	3 (1.5%)
No	103 (91.2%)	197 (98.5%)
Self-perceived economic status†		
Not enough or barely enough for basics	20 (18.0%)	84 42.0%)
Fair	49 (44.1%)	75 (37.5%)
Good or very good	42 (37.8%)	41 (20.5%)

*Difference in mean ages significant at p<.001; **difference in marital status significant at p<.001; †difference in self-perceived economic status significant at p<.001.

TABLE 2. *Mean number of incorrect answers for cases and controls at pre-test and post test.*

Study group	Mean no. (pre-test)	Mean no.(post-test)	Significance
Cases	16.12	6.96	*p* < .001
Controls	16.61	17.37	*p* > .10
Significance	*p* > .10	*p* < .001	

TABLE 3. *Linear regression model for factors related to a decrease in wrong answers given at pre-test and post-test*

Factor	Coefficient	*t*	Significance
Participation in health sessions	-8.421	-12.340	0
Age (in years)	.005	1.409	.160
Education 1	-2.104	-1.752	.081
Education 2	-1.667	-1.345	.180
Education 3	-.591	-.570	.569
Economic status 1	.571	.789	.431
Economic status 2	-.376	-.448	.655

Education 1:0=1, 2; 1=other; education 2:0=tawjihi; 1=other; education 3:0=college, university; 1=other; economic status 1:0=fair, 1=other; economic status 2:0=good, 1=other.

Pre-test

A standardized questionnaire with 86 questions was used to measure cases' and controls' knowledge of the women's health issues to be introduced in the health education sessions. A woman had the option of answering "yes", "no", or "I do not know" to each of the 86 questions. The questionnaire closely reflected the content of the 10 health education units. Cases were administered the questionnaire before the onset of their first health education session, while controls were visited at their homes and asked to respond to the questionnaire during this same period.

Cases were introduced to one of the 10 major health units and its core messages by the health educator, with one topic usually introduced per week. At one point, two messages were introduced at the same session, making for a total of 9 weekly sessions. All 113 women attended the nine sessions regularly.

Post-test

At the end of the sessions, all cases were re-administered the same questionnaire used at the pre-test. Controls were revisited at their homes where they also completed the post-test questionnaire.

Data Analysis

Descriptive and analytical statistics were performed using the Windows SPSS program. Chi-square, analysis of variance and *t*-tests were used to compare changes in responses over time. A linear regression model was also created to determine what factors influenced the outcome measure over time when other control variables were adjusted for.

Results

The average woman attending the health education sessions was 33.8±9.5 years old, married and a homemaker, with at least a primary or secondary level of education (Table 1). When asked how she perceived her economic status, she was more likely to state she felt it to be "fair" or "good". The average woman who acted as part of the control group was 39.5±12.1 years old and married. While the typical woman in the control group completed at least primary or secondary school, the percentage of women with no formal education was greater than the percentage of cases with no formal education. A woman in the control group was highly likely to be a homemaker, and when asked how she perceived her household economic status, she tended to say "not enough" or "barely enough for basics" or "fair".

Table 3 shows that cases and controls had approximately the same number of wrong answers at the initial test, with cases overall answering 16.1 of the 86 questions wrong, and controls giving 16.6 wrong answers. There were no predominant themes among the questions that both groups of women answered incorrectly, with wrong answers given in all aspects of a woman's lifecycle, as well as in regards to society's impact upon women's health and health as a human right. Wrong answers also appeared to stem from a conscious lack of experience or exposure to certain matters, such as the effect of a woman being grossly under- or overweight affecting conception, or effect of medications on male impotence.

After the nine weekly sessions were complete and the questionnaire was re-administered, the results of the post-test questionnaire showed cases significantly reduced the number of wrong answers they gave on the second questionnaire when compared to controls. Cases, or those women attending the health education sessions, answered

7.0 questions incorrectly, while controls slightly increased the number of incorrect answers to 17.4 (Table 3). The increase in controls' wrong answers was in the fields of women's rights and pregnancy.

The number of times a woman answered "don't know" to the 86 questions was also evaluated by comparing women's answers at initial test and post-test. At the pre-test, cases responded, "don't know" 4.5 times, while controls responded 4.0 times. This difference was not found to be significant. Women appeared to respond "don't know" most often for questions in which women may have had little experience, as was seen for wrong answers. For example, "don't know" appeared often when asked about issues related to miscarriage and menopause.

After women attended the health education sessions, a significant difference was found between cases and controls in the number of times "don't know" was given to a question, with cases answering 0.1 times and controls 4.4 times. To ensure that there was not an inclination for women in the community to change their answers over time, either due to outside influences or statistical tendencies towards the norm, controls' answers were compared at initial test and post-test. The results showed no significant difference overall in how the controls responded to the 86 questions, and in fact, there was a slight increase in the number of wrong answers given (Table 2).

Analysis

The mean number of incorrect answers given at pre-test and post-test was identified as the outcome variable, with participating in the health awareness sessions as the sole independent variable. Women's age and self-perceived economic status, which significantly differed between cases and controls, as well as level of education, were controlled for using linear regression. The model in Table 3 shows that when the change in currently married women's answers are examined, participating in the health awareness sessions was the only significant predictor of change in cases' and controls' answers between pre- and post-test.

Another regression model was created for all women, with women categorized as "never married" or "previously or currently married," and an interaction term between marital status and participating in the health awareness sessions added to the model as well. The results of this second model showed marital status and the interaction term to be significant (data not shown), but the model was eliminated in the final analysis due to the small proportion of subjects participating in the awareness sessions.

Discussion

The results of this paper indicate that the health awareness program was successful at increasing participant's knowledge on the women's health issues discussed over the nine-week period. By the end of the nine weeks, participants not only reduced the number of incorrect answers they gave but also appeared to exhibit confidence as seen in the significant reduction in the number of times women responded "don't know" to a given question.

The results of the linear regression model further support the awareness project's success. Participation in the awareness sessions was the only factor found to be significantly related to the reduction in the number of wrong answers between pre-test and post-test for women who were married at the time of the project. The fact that when marital status and the interaction term were added to the model, it proved to be significant shows the improvement over a period of time in answers of women who had never married compared to those currently or previously married. This finding suggests the need for another health awareness project to test the changes in responses over time between the two categories of women. This finding also stresses the importance of targeting unmarried females in health awareness programs to better prepare them to care for their health during their reproductive years. One opportunity to reach these young women is through the introduction of the appropriate topics in the school curricula.

Upon examination of the cases' wrong answers, at pre-test and post-test, one major theme appears. Questions related to women's status and their right to health care had the least reduction in the number of wrong answers between pre-test and post-test when compared to other thematic groups of questions. It would appear that the health awareness project, which only overtly deals with these issues in one unit, was unable to influence women's concepts to the same degree as other issues, such as pregnancy or menopause. The project's inability to change women's perceptions about their status in society may be due to societal norms exerting a much greater influence upon these women than an hour-long discussion. If positive change can be made in the area of women's health as a human right and their rights in society, these findings suggest community awareness projects need to intensively focus upon these issues for a prolonged period of time.

There may be several explanations for the increase in the number of wrong answers given by women serving as controls between pre- and post-test. After the first questionnaire was administered, women may have discussed the questions with family and friends, in turn negatively influencing how they answered the questions at post-test. Considering the relatively small impact the health education messages had on cases in the field of women's rights and status, it is not surprising to see women in the control group increasingly answer these questions incorrectly at post-test.

The short-term success of this intervention project is significant for several reasons. Previous research on health education in Jordan has shown that there are a number of weaknesses in the primary health care sector's ability to communicate health information to patients.[3,4] The results of this current study show that peer health educators, who themselves had little knowledge about women's health issues before being trained, were successful in changing women's knowledge in the short-term, a success similar to other studies using peer health educators.[6-9] The health educators were also able to create a positive environment for the participants and present the material in such a way that there were no dropouts over the nine-week course. This supports the idea that this type of health promotion project is sustainable because it depends upon the self-motivation of the educators and participating women, rather than incentives from outsiders.

Another reason for the success of the health education project may be due to the project coming about as a result of a larger community-based study. Rather than the researchers assuming what local women's health needs were, they were able to design an intervention project based upon the community's needs as assessed through qualitative and quantitative methods. This method of designing interventions based upon the findings of community-based studies has also proved successful in other settings.[10-14]

Training local women to act as peer health educators also allowed the local community to take ownership of the intervention program. In turn, this increased the chances of the program's success and sustainability while empowering its participants. A number of studies in developed and developing countries reaffirm the findings of this study, showing community participation not only increases intervention programs' successes, but empowers those in the community who participate in the program.[8,14-17] In this Jordanian community, empowerment was seen as a key in the short-term, and in the long-term, as a means of encouraging these women to realize their right to health care and use of the health care services at the local CHC.

This program can be implemented in the community through health centers and local women's organizations. It is a practical way for educating the general public on certain gender-specific topics, because it frees the overburdened health staff in the clinic to deal with the sick patients, and gives women the chance to contribute to their communities. Also, greater numbers of health educators can be trained on health topics according to the needs of the communities they reside in. The method is also successful because it is carried out in the homes of the health educators which provided a much more relaxed atmosphere and less rigid than a classroom in a health center or other organization. In addition, when women talk to their peers, they can relate to each other using a language that is understandable to them and they can reach women who do not usually go to the health centers or women's organizations where most of health education programs are conducted.

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HEPATOSPLENIC ABSCESSES IN PEDIATRIC ONCOLOGY PATIENTS: SIX YEARS EXPERIENCE IN A SINGLE CANCER CENTER

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Invasive fungal infections have emerged as an important cause of morbidity and mortality in immunocompromised children.[1] In the setting of prolonged neutropenia,[2,3] use of broad-spectrum intimicrobials,[4] and with the advent of chronic indwelling central venous catheters,[5-7] *Candida* species have emerged as the one of the most common causes of nosocomial infections. During the last decade, chronic disseminated candidiasis, otherwise known as hepatosplenic candidiasis, has been diagnosed with increasing frequency in immunocompromised patients. This is likely to be as a result of improvement in imaging modalities,[8,9] or changes in the presentation of systemic candidiasis.[10-12] We describe our experience of hepatosplenic candidiasis in oncology patients, focusing on the diagnosis and treatment outcome.

Materials and Method

A retrospective chart review was performed on all cases diagnosed with hepatosplenic abscesses from January 1996 to December 2001. All cases had been treated for different malignant diseases in the pediatric oncology unit at King Fahad National Guard Hospital. The criteria for inclusion in the study included antemortem diagnosis of hepatosplenic abscesses that were found by non-invasive imaging techniques (ultrasound examination or CT scan), or proven by biopsy.

Results

Six cases of hepatosplenic abscesses were diagnosed during the study period. There were five females and one male, and their ages ranged from 2 months to 11 years.

Case 1

An 11-year-old female was diagnosed with acute myeloid leukemia in November 1998. She went in complete morphological remission by the end of the second cycle of Daunomycin, Cyclophosphamide, 6-Thioguanine, Etoposide and Arabinoside-C (DCTER). She was admitted through the emergency department seven days after the 3rd cycle of DCTER with high fever, lethargy, poor feeding, loose stools and abdominal distention. Empiric treatment with broad-spectrum antibiotics was started for febrile neutropenia as per institutional policy. Her clinical condition deteriorated rapidly and she developed septic shock that required transferring her to pediatric intensive care unit (PICU) within eight hours of admission. Infectious disease consultation was obtained and her antibiotic regimen was changed from ceftazidime/gentamycin to imepenim, gentamycin and vancomycin. Blood culture grew *Klebsiella pneumoniae*. She defervesced within 48 hours and was transferred to oncology ward in stable condition. Her medications at this point included granulocyte colony stimulating factor (GCSF) and imepenim. On the 4th day of admission, she became febrile again and started to complain of anorexia. Her physical examination revealed slight tenderness in right upper quadrant, with hepatosplenomegaly. Amphotericin B (1 mg/kg/d) was added empirically on the 5th day of hospitalization because of persistent fever and neutropenia.

Laboratory findings showed neutropenia, increased alkaline phosphatase and normal serum transaminases and bilirubin. These results prompted the search for deep-seated invasive fungal infections. The results of initial abdominal ultrasound did not show any pathologic abnormality. However, CT scan of abdomen and chest showed multiple faint hypodence areas in the liver, spleen and pulmonary infiltrates. Repeat imaging a week later showed well-defined hypo-echoic lesions both in the liver and spleen on ultrasound examination (Figure 1) and on CT scan (Figure 2). The patient underwent percutaneous liver biopsy that proved negative. Because of her persistent symptoms, splenectomy and open liver biopsy were performed on the 16th day of hospitalization. Sections of liver and spleen showed granulomatous lesions, with budding yeast and pseudohyphae, consistent with the diagnosis of *Candida* hepatosplenic abscesses. Tissue cultures were negative for fungus. Ten days after starting amphotericin B therapy, the patient started to develop renal complications (rising

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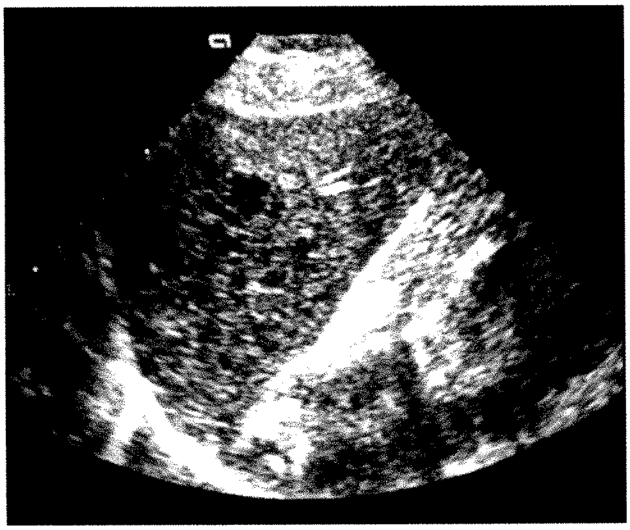

FIGURE 1. Ultrasound examination of the liver showing hypo-echoic lesions.

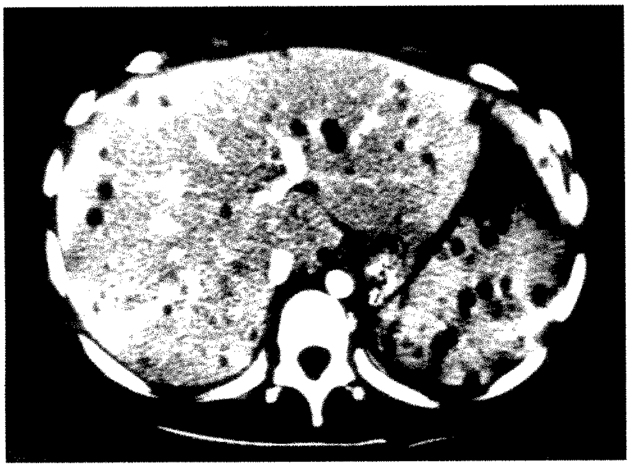

FIGURE 2. Pretreatment, CT scan of abdomen showing numerous round areas of decreased attenuation in liver and spleen, compatible with the diagnosis of hepatosplenic abscesses.

creatinine). Consequently, liposomal amphotericin B (5 mg/kg/d) was substituted for conventional amphoterin B and the patient completed six weeks of liposomal amphotericin B without complications. At the end of six weeks, she continued to show hepatic lesions, although much improved. She was discharged home on oral fluconazole (10 mg/kg/d). Repeat imaging after five months of fluconazole showed total clearance of hepatic lesions (Figure 3).

Because of her prolonged illness, the fourth cycle of DCTER was omitted. She was again admitted with febrile neutropenia after two cycles of high-dose Arabinoside-C and L-asparginase. She persistently complained of frontal headache and her physical examination showed tenderness and swelling in the region of maxillary region on the right side. CT scan examination of the sinuses revealed opacification of frontal and ethmiod sinuses along with a soft tissue mass in the right maxillary sinuses. She underwent surgical debridement with removal of the maxillary soft tissue mass. Histopathology of the mass revealed chronic inflammatory cells with multiple colonies of actinomyces and broad hyphae consistent with mucormycoses. After two weeks of liposomal amphotericin B therapy, she was discharged on penicillin and itraconazole, on the parent's request.

A month later she was again admitted with headache, blurred vision and poor appetite. Lumber puncture was carried out and revealed blasts in her spinal fluid. A decision was made to re-induce her and consolidate with allogenic bone marrow transplant, but unfortunately the parents refused further management. She died after a month, approximately eight months from the date of diagnosis as a result of relapsed myeloid leukemia.

Case 2

A six-month-old female child was diagnosed with acute myeloid leukemia in September 1997, when she presented with hepatosplenomegaly and was found to have neutropenia. Bone marrow aspirate revealed myelofibrosis with excess blasts. One week after receiving the first cycle of DCTER, she was admitted to PICU with fever, loose stools and evidence of disseminated intravascular coagulapathy (DIC). She was found to be neutropenic. Ceftazidime, gentamycin and clindamycin were initiated. Amphotericin B was added on the 5th day of fever. The neutropenia subsided, however the fever persisted. Abdominal ultrasound was done which showed multiple hypo-echoic areas in the liver and spleen. A CT scan of sinuses, chest, abdomen and pelvis revealed faint hypo-dense lesions in liver and spleen. Urine culture grew *Candida albicans*. She was treated for six weeks with amphotericin B combined with 5-flurocytosine (5-FC) for the initial two weeks. She was discharged on oral fluconazole to continue until all lesions disappear or calcify. During the rest of chemotherapy during periods of febrile neutropenia, she received additional Amphotericin B until neutropenia resolved. She completed chemotherapy in April 1998 and a follow-up scan 18 months later demonstrated calcified areas in the liver and spleen. The patient is alive with no evidence of hepatosplenic abscesses.

Case 3

A three-year-old girl with Down syndrome presented with epistaxis, fever and weight loss, and was diagnosed to have with acute myeloid leukemia in May 2000. Ten days after she received her first cycle of induction therapy (DCTER), she was admitted to PICU with high-grade fever, gingival bleeding, retrosternal pain, hepatosplenomegaly and shock. She was found to have neutropenia. During her hospitalization, she had a complicated course where she

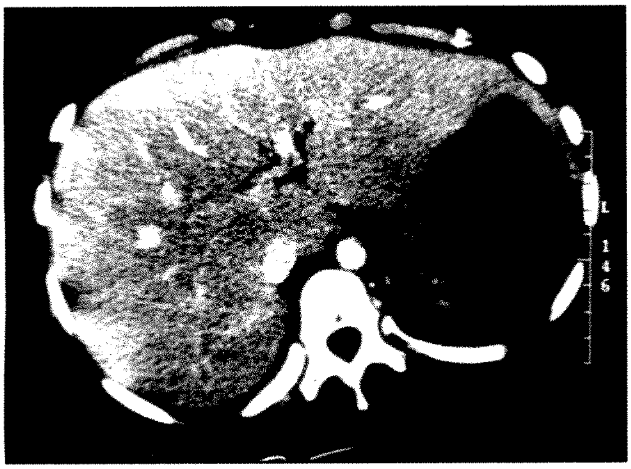

FIGURE 3. Post-splenectomy CT scan of abdomen showing complete resolution of hepatic lesions.

developed *E. coli* and *Enterococcus* urinary tract infection, bronchopneumonia and herpes simplex virus type 1 mucositis. Because of persistent fever, nausea and hepatosplenomegaly, a CT scan of abdomen was done and showed hepatosplenic hypo-dense lesions thought to represent abscesses. A diagnostic biopsy was offered but refused by the parents. After six weeks of amphotericin B, a repeat CT scan showed improvement in the hepatosplenic lesions. She was discharged on oral fluconazole. Unfortunately, in April 2001 she was admitted with left hemiperesis and was found to have right middle cerebral artery infarct secondary to antiphospholipid antibodies. Two months later she presented with thrombocytopenia while still on therapy, and died of bone marrow relapse in August 2001, 14 months after diagnosis.

Case 4

A five-year-old female was diagnosed with myelodysplastic syndrome (MDS) type refractory anemia with excess blasts in transformation (RAEBt) in July 2000. She underwent induction therapy, and went in remission after 4 cycles of DCTER. She was admitted with fever and gingival bleeding in January 2001, a week after receiving high-dose Cytarabine and L-asparginase. She was severely neutropenic on admission. Her fever persisted despite the administration of appropriate antibiotics. A CT scan of sinuses, chest, abdomen and pelvis revealed pulmonary infiltrates in both lower lobes. Amphotericin B was added. A repeat scan two weeks later at the onset of neutrophil recovery showed improvement in the pulmonary infiltrates, along with the appearance of hypo-dense lesions in the liver and spleen, consistent with the diagnosis of hepatosplenic abscesses. The parents refused liver biopsy. The patient could not tolerate conventional amphotericin B and was replaced with liposomal amphotericin for seven weeks. A follow-up CT scan two months later showed complete resolution of the hepatosplenic abscesses. She relapsed six months after the completion of therapy in October 2001. She was re-induced with mitoxantrone and etoposide and underwent allogenic bone marrow transplant in November 2001. She remained alive and well at the time of the study.

Case 5

A six-year-old female was diagnosed with acute myeloid leukemia in September 1997, when she presented with splenomegaly and found to have neutropenia. She was admitted two weeks after receiving second cycle of induction with fever, multiple skin abscesses, and clinical sepsis. On admission, she was severely pancytopenic. She received ceftazidime, amikacin as empiric antibiotic coverage. Vancomycin was added because of *Staphylococcus epidermidis* bacteremia. The fever persisted, and on the 5th day Amphotericin B (1 mg/kg/day) was added for fungal prophylaxis. She underwent skin biopsy that showed chronic inflammatory changes with no leukemic infiltrates. Skin biopsy specimen grew *Acinotobacter,* which was sensitive to imepenim and gentamycin. CT scan revealed bilateral pulmonary infiltrates, extensive multiple hypo-dense lesions in the liver, spleen and kidneys and opacity of maxillary sinuses. She recovered from her illness and after four weeks of AMPHOTERICIN B, pulmonary, renal and sinuses lesions had cleared, however hepatosplenic lesions became more numerous and discrete. In January 1998, she underwent splenectomy and open liver biopsy. Section of liver biopsy showed multiple micro-abscesses with fungal hyphae consistent with *Aspergillus*. Tissue cultures of liver and spleen were negative. Because of persistent hepatic abscesses, conventional amphotericin B was changed to liposomal amphotericin B (2 mg/kg/day), which was given for three weeks. In February 1998, chemotherapy was resumed and she received two cycles of intensification (Ara-C, L-Asp) and discharged on oral itraconazole. In March 1998, her follow up scans showed improvement of hepatic lesions. She completed chemotherapy in June 1998. Two months later she was again admitted with limping and was found to have multiple lytic lesions in tibia and fibula. Skeletal survey showed multiple lytic areas in long bones, skull, iliac, shoulder and vertebrae. Bone and Gallium scan showed increased tracer uptake in these lytic areas. Biopsy from the humerus showed granulomatous inflammation with focal collection of fungal hyphae consistent with *Aspergillus*. She again received additional Amphotericin B for five weeks for fungal osteomyelitis and discharged on itraconazole. A follow-up scan in March 1999, showed widespread hepatic calcification. Itraconazole was discontinued in September 2002, after a negative total body Gallium scans.

Case 6

A four-year-old male was diagnosed with neuroblastoma (NBL) in July 1995, when he presented with abdominal mass. He was admitted in April 1996 with febrile neutropenia after receiving Cisplatin, Doxoribicin, Etoposide and Ifosfamide. Fever defervesced within 48 hours of initiation of antibiotics. At the onset of neutrophil recovery, he started to experience anorexia and right upper quadrant pain. His serum alkaline phosphatase level started to rise. A CT scan of abdomen revealed multiple 2-3 mm size hypo-dense lesions in the liver and spleen, consistent with the diagnosis of hepatosplenic abscesses. He received amphotericin B for six weeks and had a follow-up CT scan in June 1996 that demonstrated complete resolution of hepatic lesions but persistent splenic lesions. He underwent splenectomy in September 1996. Histopathology sections revealed areas of central necrosis with surrounding granulomatous inflammation and positive fugal staining showing hyphae consistent with *Candida*, however tissue culture remained negative for fungi. He completed chemotherapy in December 1996 and remained free of evidence of hepatic candidiasis. On August 1997, his disease relapsed. He then received Ifosfamide, Carboplatin and Etoposide (ICE) and local radiotherapy, but unfortunately the tumor started to grow and he finally died in January 1999 of the primary disease.

Discussion

Invasive fungal infections, which are mostly caused by Candida and *Aspergillus*, are a major threat to the survival of neutropenic patients receiving treatment for hematologic malignancy or solid tumors. Damage to the mucosa allows colonizing organisms, especially *Candida* organisms, to invade tissue and enter the blood stream. These factors, coupled with antibiotic usage suppresses the normal bacterial flora, and allows fungal overgrowth to increase the risk of invasive fungal infections. Certain immunosuppressive drugs, including corticosteroids can suppress cell-mediated immunity and enhance susceptibility to invasive fungal infections. *C. albicans* has historically been the leading fungal pathogen in oncology patients. Thaler et al. reported it as the most frequent cause of hepatosplenic candidiasis (20 out of 31 *Candida* isolates), followed by *C. tropicalis*, and one each of C. *pseudotropicalis and C. stellatoidea.*[11] However, *C albicans* infection in neutropenic patients has dropped with the use of prophylactic fluconazole, and there is an increase in the incidence of infection with fluconasole-resistant *C. krusei* and *C. glabrata* species.[4]

Manifestation of candidial infections are protean, ranging from acute, life-threatening disseminated candidemia to chronic disseminated candidiasis, otherwise known as hepatosplenic candidiasis. Hepatosplenic candidiasis is characterized by disseminated candidiasis often without detectable fungemia, in a hemodynamically stable patient and carries high survival rate when antifungal therapy is administered. The constellation of fever, abdominal symptoms, and elevated alkaline phosphatase level in a patient with cancer recently recovering from an episode of granulocytopenia is highly suggestive of this entity and should prompt the treating physician for a diagnostic imaging and biopsy. All of our patients had fever and five of them had hepatosplenomegaly. Alkaline phosphatase was raised in five patients.

The origin of infection seems unknown; presumably it occurs as a result of hematogenous spread or through the entrohepatic circulation while the patient is neutropenic. Fever might be the only symptom, as it may go unnoticed for a protracted period of time without localizing signs.

Of late, there has been a notably increase in the incidence of hepatosplenic candidiasis. Does this increase present a real increase in the disease incidence or merely an appreciation of this syndrome? Indeed, there are some important clues that might explain this observation. First, there is an increase in number of immunocompromised patient at risk of developing this disease because of the more frequent use of intensive chemotherapy protocols. Second, with the concomitant use of better antimicrobials and blood product support, more patients survive the state of fever and neutropenia to a point where the manifestations of hepatosplenic candidiasis can be diagnosed. Third is the more frequent use of noninvasive imaging studies, particularly ultrasound and high-resolution abdominal CT scan in a patient at high risk of developing this syndrome, making the diagnosis earlier. Fourth is the improved supportive care and judicious use of amphotericin B early in the course of neutropenia which may actually result in evolution of acute disseminated candidiasis, a fatal infection in the past if left untreated, into a more indolent disease like hepatosplenic candidiasis.[10,12]

Traditionally, non-invasive techniques such as abdominal ultrasound examination and CT scan can be highly suggestive of hepatosplenic candidiasis in a patient with persistent fever and abdominal symptoms who is recovering from neutropenia, but no one technique is diagnostic.[10,13] False-negative results of these studies are not uncommon and can be attributed to their inability to detect very small lesion or the inability of a neutropenic host to mount an inflammatory response that can be detected by these studies. Thus, repeat examination is warranted in such a clinical setting. Moreover, the CT or ultrasound scan finding might be variable in different patients over time. For example, some patient might show hypoechogenic lesions, others have lesions in concentric layers with characteristic bulls eye lesions, or show dense calcified centers. Thus the natural course and pathological abnormalities associated with hepatic candidiasis make the diagnosis difficult.[11]

The diagnosis of hepatosplenic candidiasis is critical. It requires a high degree of suspicion and diligence. In the right clinical scenario, a negative ultrasonic or CT scan examination should prompt a more invasive technique for diagnosis. Biopsy by mini-laparotomy or peritoneoscopy may be necessary.[14] If nodules are found, careful histologic examination is necessary. Fungal elements can still be missed unless the central core of the nodule is examined by wet mount and special fungal stains, searching for centrally located yeast or pseudohyphae. Diagnostic confirmation requires positive growth of *Candida* isolates. Again, false-negative results may be a problem, either because of sampling techniques or as a result of previous exposure to amphotericin B, which may inhibit fungal growth *in vitro*. Since many patients have received amphotericin B in the past, it is not surprising that positive cultures are uncommon.[11]

Biopsy of hepatic lesions is important for several reasons. First, other disease process like malignancy may simulate lesions of hepatosplenic candidiasis. Second, the administration of long-term amphotericin B is justified only with definite evidence of candidiasis, and third, biopsy confirmation may be necessary for the delivery of lipid formulation of amphotericin B in refractory cases. Biopsy was done in three of our patients; two had a fungal staining suggestive of *Candida* and one suggestive of *Aspergillus*. None had a positive culture. The number of patients with biopsy proven hepatosplenic candidiasis in our series is small (2 out of 6). This is explained by the difficulty in doing invasive procedures in this type of patients, and in some situations, the parent's refusal of these procedures. It is well known that the yield from such procedures in diagnosing fungal infections is not optimal. This supports the effort to find an alternative easier way to do diagnostic methods such as molecular technology. Therefore, reliance on clinical findings as well as response to therapy remains the major way of management.

Amphotericin B remains the gold standard mode of therapy.[15,16] The recommended duration of therapy for hepatosplenic candidiasis ranges from 6-12 weeks depending on the response. Although controlled clinical trials have not addressed the value of combined amphotericin B and 5-FC, some investigators have suggested this combination to be more beneficial than monotherapy with amphotericin B alone.[17] Our initial approach in managing hepatosplenic candidiasis is administration of amphotericin B (1 mg/kg/day) for a total of 6 weeks, followed by a long-term fluconazole (6-10 mg/kg/day) therapy until complete resolution or calcifications. As shown in our study, some patients may still have residual active infection even after completion of treatment. These patients pose the dilemma of prolonged anti-fungal therapy. Ideally, if it seems possible further immunosuppressive therapy may be withheld until all the lesions are calcified. However, in clinical settings this option seems far from reality, as underlying malignant process may not permit. These are the patients who need both modalities concurrently.

With the availability of lipid formulations of amphotericin B, a strategy of reticuloendothelial loading has led to completion of a phase 1-2 protocol using amphotericin B lipid complex (ABLC) for the treatment of hepatosplenic candidiasis.[18] Recent developments in anti-fungal therapeutics have led to introduction of third-generation triazoles and echinocandins.[17,19] Among the third-generation triazoles, voriconazole is the most clinically tried. Characterized by parenteral and oral formulations with broad antifungal spectrum against yeast and filamentous fungi, voriconazole is being studied for the prevention and treatment of life-threatening mycoses in patients with cancer and those undergoing bone-marrow transplantation.[19] The echinocandins are cyclic lipopeptides, which inhibit fungal cell wall biosynthesis. Related to the target specificity, these compounds appear to have an excellent safety profile. With activity against *Candida* spp. as well as *Aspergmus* spp., echinocandins are being studied for the treatment of candidemia and for the prevention of fungal infections in immunocompromised patients.[19]

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Letters to the Editor

Hepatitis B Virus Serum Markers among Pregnant Women in Sana'a, Yemen

To the Editor: A variety of congenital viral infections are responsible for a large proportion of mortality and morbidity in infancy and childhood. Hepatitis B virus (HBV) is recognized as one of the important viruses transmitted transplacentally.[1] Transmission of HBV from mother to infant plays an important role in the maintenance of endemicity, especially in regions where such infections are hyperendemic.[2] Since a large fraction of vertical infection progresses to chronicity,[2] infected infants can initiate new cycles of both horizontal and vertical infection.[3] In addition, transmission of HBV from positive carrier mothers to their infants may result in neonatal fulminant hepatitis B infection.[4]

Yemen lies within the geographical region where HBV infection is highly endemic. Several seroepidemiological surveys of hepatitis B have been conducted in Yemen. These studies showed a high prevalence of hepatitis B infections among the general population and high-risk groups ranging from 13.2% to 18.5 %, using HB surface antigen as indicators.[5-8] Furthermore, Scott et al. and El-Guneid et al., in two separate studies, found that up to 50% of study populations were positive for at least one serological marker of HBV.[6,7] Also, Al-Shamahy in his study on the risk factors affecting the transmission of HBV among mothers in Yemen, found a significant risk associated with history of blood transfusion, hospitalization and surgery.[5]

In Yemen, there is no standard policy for the prevention of HBV transmission, but a universal immunization for infants was introduced in early 2000 and was expected to cover all the country in the following two years.

The main goal of the current study was to determine the prevalence of HBV markers between a sample of pregnant women in Sana'a city, and the chance of vertical transmission of HBV. This would make it possible to initiate hepatitis B screening of pregnant women attending prenatal clinics and afford both HBV vaccination and immunoglobulin (HBIg) for their newborn babies to minimize the risk of vertical transmission.

Cross-sectional survey was conducted from 1st June to 30th of October 1999 in Sana'a city. A total of 182 pregnant women were selected by a systematic sampling of pregnant woman attending prenatal care clinics in Sana'a. Only females who had no acute illness requiring bed-rest, and who provided informed consent, were enrolled. Volunteers answered a brief demographic questionnaire and venous blood was taken from all them. Based on prior reports of HBsAg prevalence of 12% and the worst acceptable value of 4%, not less than 178 randomly selected subjects were needed out of the total estimated 200,000 females over the age of 15 years in Sana'a city at a confidence level of 99.9%.

The ELISA technique was used to examine serum samples for hepatitis B surface antigen (HBsAg), hepatitis *e* antigen (HBeAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb) and hepatitis B *e* antibody (HBeAb) with commercially available kits. Specimens, which repeatedly proved reactive by ELISA in two separate tests, were considered positive. Data was analyzed using EPI-Info version 6.

A total of 182 volunteers completed the study questionnaire and donated blood. The age of volunteers ranged from 20 years to 39 years .The mean age of volunteers was 26.8 years. All volunteers were pregnant, non-vaccinated for HBV and living in Sana'a city.

Serological test results are recorded in Tables 1 and 2. A total of 35.2% of the study population was positive for at least one serum marker of HBV infection. The seroprevalence among pregnant women was 6.6% for HBsAg, 3.8% for HBeAg, 16.5% for HBcAb, 17.6% for HBsAb and 10% for HBeAb (Table 1).

When the age of pregnant women was considered as predisposing factor for hepatitis B virus infection, HBcAb was selected as an indicator of exposure to HBV. There was a significant effect of older age on contracting hepatitis B virus and a high significance when compared with the younger age groups (Table 2).

Discussion

Neonatal infection with hepatitis B virus carries a very high risk of resulting in a persistent infection. Babies born to hepatitis B carrier mothers are at risk of infection through exposure to blood and body fluids during birth.[9] These at-risk babies can only be identified through screening of all mothers during pregnancy. Prevention of infection in this group is a key element in any national strategy to reduce the incidence and eventually eliminate hepatitis B infection in its population, as the persistently infected infants act as a reservoir of infection throughout their lives.[10] The prenatal transmission of hepatitis B virus from mother to child can be effectively prevented by the combined administration of HB immunoglobulin (HBIg) and hepatitis B vaccine (HB vaccine) immediately after birth.[11,12]

There has been inadequate information on the prevalence of viral hepatitis B serological markers among pregnant women in Yemen. The prevalence of HBsAg among our subjects was 6.6%, of anti-HBs antibody 17.6%, of total anti-HBc antibody 16.5%, of HBeAg 3.8%, and of anti-HBe antibody 10% (Table 1). The prevalence of markers in our study was lower than that reported among pregnant Albanian refugees, where the prevalence of HbsAg was 13.4%, of anti-HBs antibody was 53%, of total anti-HBc antibody was 70%, and of anti-HBe antibody was 58%. However the profile HBeAg was higher in our study

TABLE 1. *The prevalence rate of hepatitis B virus markers among pregnant women in Sana'a city, Yemen, 1999.*

Markers	HBsAg	HbeAg	HbsAb	HbeAb	HbcAb	Total*
Positive (no.)	12	7	32	18	30	64
Positive (%)	6.6	3.8	17.6	10	16.5	35.2

*Positive at least for one serum marker of HBV.

TABLE 2. *Past exposure of hepatitis B virus among a sample of pregnant women in Sana'a city, Yemen 1999 by age.*

	Positive HBc antibody			
Age group (year)	No.	%	OR	*P*-value
20 to 25 (n=76)	5	6.6	0.23	0.002
26 to 30 (n=78)	15	19.2	1.4	0.38
+31 (n=34)	10	29.4	2.7	0.024
Total (n=182)	30	16.5		

OR=odds ratio.

(3.8%) than in the Albanian refugees study (1.2%).[13] In Algeria, the prevalence of HBsAg and anti-HBc antibodies among pregnant women was 1.6% and 11.1%, respectively, and these are lower than that reported in our study.[14]

In our study, the prevalence rate of HBs antigen as a marker for carrier state (6.6%) was lower than that reported previously among mothers in Sana'a Yemen which was estimated to be between 13.2% and 18.5%(5-8); and among pregnant Albanian refugee (13.4%).13 However, the prevalence in our study was higher than what has been reported among mothers in Saudi Arabia which was estimated to be between 2.3% and 5.4% (HBsAg),[15-17] and much higher than among pregnant women in Algeria (1.6%),[14] and in Mexico (1.8%-0.26%).[10] In addition, the true rate of HBsAg among our subjects may be more than 6.6% because of the phenomenon of window phase of infection which occurs as a result of the increase of anti-HBs antibody, which may result from the formation of Ag-Ab complexes whose components are not detected by serological testing.[18]

The prevalence of HBsAg noted in this asymptomatic population might reflect chronic HBV infection (HBV chronic carrier). In addition to that all HBsAg positive pregnant women in our study should be considered potentially infectious, and the relative degree of their infectivity was assessed by determination of HBeAg. The profile of HBsAg and HBeAg (HBsAg + HBeAg) was 3.8% where 58.3% of HBsAg positive mothers were positive for HBeAg. The rate of HBeAg positive among HBV carriers in our subjects was almost similar to that reported previously in Yemen by Abdel-Raheem and others (50%),[8] but more than that reported by El-Guneid and others (32.1%).[6]

The likelihood that HBeAg is present in persons with chronic HBV infection may vary in different populations because of the age at which chronic infection occurs and the age-dependent rate of HBeAg clearance.[19,20] The prevalence rate of HBeAg positivity among our subjects in Yemen (3.8%) is similar to the low range of its prevalence among general population in Middle East and Africa (5%-10%), where the prenatal HBV transmission is not common. However, it is very low compared with the range of Southeast Asia (20%-30%) which results in high rates of prenatal HBV transmission.[21]

It is obvious that 58% of chronic asymptomatic carriers pregnant women in our study show evidence of high infectivity where they are positive for HBe Ag which is known to be responsible for infectivity. Probably 90% of these mothers could be expected to transmit HBV to their infants and 85%-90% of them will become chronic carriers.[22]

In our study, about 17% of the subjects were positive for anti-HBc and anti-HBsAg antibodies, which is usually the result of HBV infection and will persist for a lifetime of pregnant women with resolved infection.

At least 35.2% of the study population was positive for at least one serum marker of HBV and this result is less than the earlier reports by El-Guneid and others and Scott and others.[6,8] In addition, the prevalence of HBV markers noted in these asymptomatic population may have been due to either past sub-clinical or current active sub-clinical disease or to exposure to antigens without active disease.

In our study, the prevalence of HBcAb as an indicator for exposure to HBV increased with age among the pregnant women in the 30+ age group, where it reached up to 29.4% (OR=2.7, P=0.024) (Table 2). This increase could indicate an accumulated risk of infection over time. In addition, the results indicated that the horizontal spread of hepatitis B virus among our subjects is very common.

The high prevalence of hepatitis B markers in pregnant Yemeni women may indicate that HBV infection is endemic in Yemen, and the possibility of prenatal transmission to offspring urges the requirement for screening of all mothers during pregnancy. Infants delivered to HBsAg seropositive mothers should also receive HBIg and HBV vaccine immediately after birth, and this should be integrated with an immunization program against HBV in Yemen. Further research, coupled with study of spouses and offspring (e.g., cord blood sample) is recommended.

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Chorea can Present Long Before Other Manifestations of Primary Antiphospholipid Syndrome

To the Editor: A 42-year-old lady presented with acute blue discoloration and ulceration of the left toe. She had also been complaining of a bluish discoloration and pain of all her toes, which were cold, induced for the past three months.

The patient has been complaining of involuntary movements that started nearly 20 years ago. They involved both upper and lower limbs on both sides. Initially they were jerky, persistent and embarrassing, but later on became intermittent, and less obvious to the surrounding people.

In 1994, she had a stroke with a cerebral infarct involving the left posterior parietal lobe and micro-infarcts scattered in the white matter, manifested as dysphasia and right facial weakness. The stroke was preceded by few transient ischemic attacks with transient muscle weakness, numbness and amaurosis fugax. In the past few years, she was noticed to have levido reticularis rash, and occasional polyarthralgia. On one occasion she was found to have transient thrombocytopenia. She developed hypertension at the age of 20, but a thorough work-up of secondary hypertension did not reveal any abnormality. She is a mother of six children. She had one stillbirth at eight months of pregnancy, but there was no history of miscarriages. A diagnosis of mitral valve prolapse without a regurge was made based on an echocardiogram in 1994. The patient did not show any symptoms suggestive of systemic lupus erythematosus or any other connective tissue disease. She was on baby aspirin once daily, persentine and a daily dose of 50 mg atenolol to control the blood pressure.

During the physical examination, she was experiencing involuntary fine movements of both upper and lower limbs which sometimes became jerky. The blood pressure was well controlled. The peripheries were cold and the left second toe had a dark blue color (Figure 1) with an ulcer at the tip (Figure 2). The rest of the digits including the toes and the fingers looked bluish. There were no further areas of ulceration or infarct and there was no telangiectasia or capillary dilatation at the nail bed. Peripheral pulses were normal. There was a levido reticularis rash noticed on both upper and lower limbs. Examination of the heart revealed a mitral valve click with no murmur. The rest of the examination including the musculoskeletal, the abdomen and CNS was unremarkable.

Investigations revealed a normal hemogram (platelets 165), electrolytes, creatinine and liver enzymes. ESR was 20 and C-reactive protein was normal. Activated partial thromboplastin time (aPTT) was 62 with a control of 32.

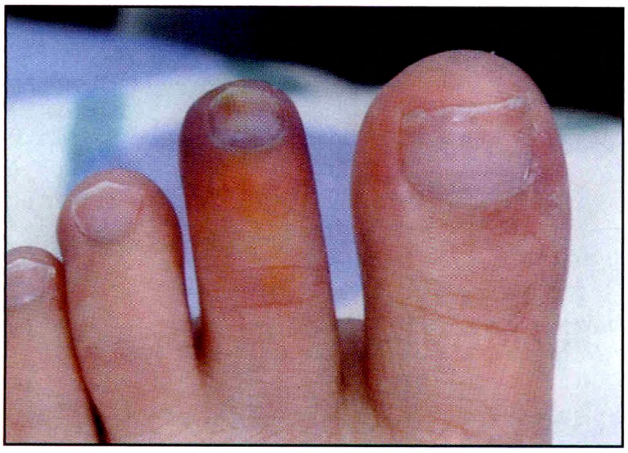

FIGURE 1. The left second toe which had a dark blue appearance.

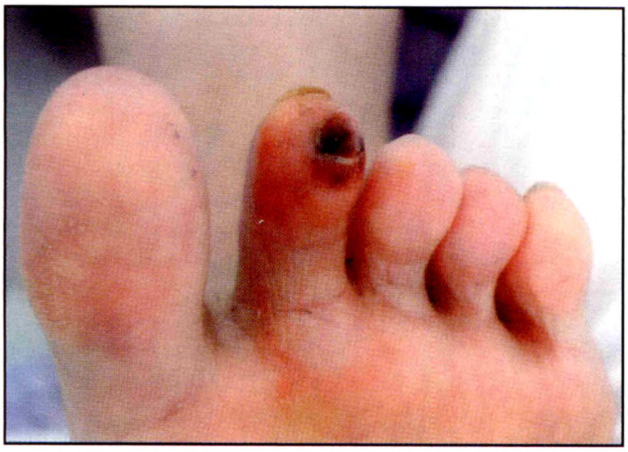

FIGURE 2. Ulceration at the tip of the toe.

The prothrombin time (PT) and the international normalized ratio (INR) were normal. Anticardiolipin antibodies were as follows: IgG 127, IgM normal and IgA 42 with an upper limit of normal being 15. Lupus anticoagulant was weakly positive. Antinuclear antibodies and anti-double stranded DNA were both negative. Protein C, protein S and anti-thrombin III were all negative. Hepatitis screen and antineutrophilic cytoplasmic antibodies (ANCA) were negative. A transthoracic echocardiogram showed a mitral valve prolapse with no regurge and no vegetations. A vascular study of the lower limbs with a cold provocation test showed a noticeable impairment in the digital arterial flow for most of the digits. Doppler of the carotid arteries and the upper limb vasculature was normal.

The patient was given a diagnosis of primary antiphospholipid syndrome (APS) and treatment with low molecular weight heparin was commenced. Warfarin was also started. Based on the history of exaggerated vasospasm on cold exposure which was confirmed by the vascular study, she was also treated with prostacyclin (iloprost) infusion. Atenolol was replaced with diltiazem because of the presumptive aggravating effect of B-blockers on vasculopathy.

A few days after initiating therapy, the patient started to show an improvement in the color of her digits except for the second toe, which remained slightly blue with the ulcer gradually healing, although over a long period of time. The levido reticularis rash remained the same. The patient continued to experience the involuntary movements during her stay in the hospital and upon discharge. The INR was kept around 3.5. A discussion was carried out with the patient regarding initiating therapy for the choreatic movements but she preferred not to start treatment claiming that she was adapting well to the problem.

Discussion

This is a case of primary APS fulfilling the Sapporo criteria for the diagnosis of APS.[1] Her disease initially manifested as stroke, migraine headaches, arthralgia, digital ischemia and ulceration, levido reticularis, and thrombocytopenia, although transient.

Neurological manifestations are known to accompany APS. Chorea, although is one of the diagnostic clinical criteria, is rarely seen and reported in association with this syndrome. It can occur in both primary and secondary APS.[2,3] In a large cohort study, in which they reviewed the clinical manifestations of APS in 1,000 patients from 13 European countries, they found that chorea was present in 1.3% of their patients. They also found that chorea mostly occurred before the age of 15.[4] Other studies have also documented its appearance in the young population and suggested considering APS in the work-up of patients presenting with chorea.[5-8] Chorea can also be one of the manifestations of systemic lupus erythematosus (SLE). Our patient, however, did not show enough criteria for the diagnosis of SLE or any other associated connective tissue disease.

Chorea is mostly reversible with treatment but can sometimes be persistent.[9] The pathogenesis might be different in those two conditions. It has been hypothesized that in reversible chorea, striatal binding of antiphospholipid antibodies (aPL) results in dysfunction while in persistent chorea, aPL-associated striatal ischemia has been postulated.[2] The former hypothesis is supported by the transient hypermetabolism in the contralateral basal ganglia shown on positron emission tomography (PET) done on serial patients suggesting an excitatory rather than ischemic pathogenesis.[10,11]

In a review of 50 patients with chorea and APS, 96% of the patients were female, 58% had SLE and 30% had primary APS. Their mean age at presentation of chorea was 21±12 years. It was bilateral in 55% of the patients. Twenty percent of the patients developed chorea soon after starting estrogen-containing oral contraceptives, during pregnancy, or shortly after delivery, suggesting a potential role of estrogen in this disorder.[9]

Treatment of APS associated chorea has been tried with a variety of medications and in some with success, including steroids, haloperidol, antiaggregants, anticoagulants[9,12] and immunosuppressive agents such as hydroxycholoroquine and methotrexate.[13,14] Our patient preferred not to try any therapeutic agent to control the movements since she had been adapting psychologically and socially to the problem.

We suggest that APS should be recognized as one of the serious underlying problems that have to be worked up and treated in any patient presenting with chorea even without having other manifestations of APS concurrently. Appropriate approach of this problem can save the patient from thromboembolic events that can sometimes be fatal.

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Drug Use and Acute Abdomen

To the Editor: Gastrointestinal symptoms (Table 1) are common among illicit drug users.[1] These are either due to pharmacological actions of certain illicit drugs, or they occur during withdrawal from others. A more striking presentation like acute abdomen suggesting perforation or peritonitis is extremely rare. Few cases of this have been described in literature.[2-7] The etiology varies with the drug being abused. In heroin users, narcotic bowel syndrome, intestinal obstruction and inflammation are blamed for the acute abdomen. In alcoholics, upper GI bleeding and acute pancreatitis are held responsible while in stimulant users, ischemic perforation and inflammation of the gut are implicated.

Three cases of acute abdomen in drug users are being presented. These were seen in a 12-month period between January and December 2000 at Al Amal Hospital in Jeddah, which is an institution that specializes in addiction treatment.

Case 1

A 25-year-old, smoker, glue-dependent male presented to the OPD with acute generalized abdominal pain of few hours duration. Pain was localized in the epigastrium and radiated to the right upper quadrant and back. Past medical history was insignificant. He denied any trauma. On examination he appeared in severe discomfort and was barely able to walk. Vital signs were normal. There was generalized abdominal tenderness, guarding and rebound. Upright plain x-ray abdomen revealed gas under the right diaphragm. He was immediately referred to the general hospital for surgical management.

Case 2

A 37-year-old, smoker, IV heroin-dependent male was admitted for management of heroin withdrawal. Past medical history was significant for a duodenal ulcer two years earlier that was managed conservatively. He denied any trauma. The withdrawal symptoms were treated symptomatically with Thioridazine 25mg t.i.d and Brufen 400mg t.i.d. He received prophylactic Ranitidine 150mg b.i.d.

On the second day, he developed vomiting and continuous peri-umblical pain. Abdominal examination was

TABLE 1. *Gastrointestinal problems in drug users.*

	Opiates	Alcohol	Stimulants	Cannabis	Benzodiazepines	Volatiles	Nicotine
During withdrawal	Nausea Vomiting Diarrhea Cramps	Nausea Diarrhea	–	–	Anorexia Nausea Vomiting	–	Stomach distress Constipation
With intoxication	Nausea Vomiting Constipation	Acute pancreatitis Gastritis Diarrhea	Nausea Vomiting Anorexia bowel ischemia gangrene	Dry mouth Increased appetite Antiemetic	–	–	Anorexia
In chronic users	Constipation	Gastric ulcer cirrhosis	Weight loss	–	–	Hepato-toxicity	Weight loss

unremarkable. Vital signs were normal. Blood count, electrolytes and liver function tests were within normal.

Abdominal pain was treated with Buscopan injection 10 mg but 12 hours later, the pain had worsened with constipation. He was given Buscopan tablet 10 mg, laxatives, IV fluids and Diclofenac injection 50 mg IM stat. Surgical consultation was also sought, but the pain had localized to the right iliac fossa. Abdomen was tender but without guarding or rebound. Acute appendicitis was suspected. He was given a second injection of Diclofenac 50 mg IM. X-ray of abdomen showed gas under the right diaphragm. He was transferred to general hospital for surgical management.

Case 3

A 46-year-old, smoker, heroin-dependent male was admitted for detoxification. Past medical history was insignificant. He denied any history of trauma. Heroin withdrawal was treated symptomatically with Thioridazine 25 mg t.i.d and Brufen 400 mg t.i.d. Investigations revealed WBC of 12800, ESR 48, abnormal liver function tests (bilirubin, ALT and alkaline phosphatase raised to less than twice the normal limit) and positive serology for HCV.

On the fifth day, he developed generalized abdominal pain that was treated symptomatically with oral Buscopan 10 mg. About 12 hours later, the pain had worsened. It was more intense, persistent, localized to right upper quadrant and referred to right shoulder. He was unable to lie flat. Abdomen was tender, distended without guarding or rebound. Vital signs were normal. X-ray of abdomen showed gas under the right diaphragm. He was referred to general hospital for surgical management. Repeat x-ray of abdomen was normal. He underwent immediate endoscopic examination. This revealed esophageal varices, gastritis and fresh blood in the gastric secretions. No perforation was visible. It was assumed he bled from the varices. He was managed conservatively.

These cases were Saudi men. The hospital does not treat females. Surgical exploration revealed sealed ulcer perforation in two cases. The first patient was very young. Besides smoking he had no other predisposing factors for ulcer.[3,8,9] There are three possible explanations of perforation in this case.

Perforated ulcers are known to be associated with *H. pylori* infection.[8-11] The infection is common in third world countries particularly among young adults. It is possible that this patient had *H. pylori* infection. Self-neglect and poor physical health is commonly seen in drug users. Concurrent medical illnesses and infections are frequent.[12,13] It is therefore plausible that *H. pylori* infections are also more prevalent in drug users. Further studies are needed to verify this. The second explanation is that perforation was caused by glue. Inhalants as a group are not known to be ulcerogenic. Acute abdomen had never been reported before with glue dependency. Glue is a mixture of complex volatile compounds.[1] During inhalation, some of the glue invariably also gets ingested. It is possible that an ingredient or combination of ingredients in the ingested glue may be directly toxic to the stomach or guts lining causing ulceration or erosions. Lastly inhalant use increases cathecolamine release that produces vasospasm. In the long term, sustained and elevated circulating cathecolamine levels may ultimately damage the vascular endothelium. Regular use of inhalants over the years could therefore lead to ischemic damage of the gut that may eventually result in perforation. The association of inhalant use and peptic ulceration requires further investigation.

In contrast, the second patient had several predisposing factors.[8-11,14] The assumption was that a silent ulcer complicated by NSAIDs caused the acute abdomen. However, some of the evidence goes against this possibility. The patient was under 40 years. He was asymptomatic prior to admission, the treatment duration was very short and he was given prophylactic Ranitidine during hospitalization. Two concurrent NSAIDs (Brufen tablets and Diclofenac injections) were prescribed but the second NSAID was given after the onset of acute symptoms. The dose of both medicines was within the recommended range of formulary. NSAID use was neither injudicious nor indiscreet. It was most likely a combination of non-iatrogenic factors like smoking, psychological stress and heroin use that determined the clinical presentation.[15,16]

The third case was different. He had alcohol related cirrhosis and possibly HCV hepatitis. Bleeding varices could have caused the acute abdomen but the vital signs were stable, and there was no history of melena. The most likely explanation of acute abdomen in this case is narcotic bowel syndrome. This condition clinically resembles acute abdomen with viscera perforation.[4] There is no explanation of why free air was present in the abdomen on first x-ray.

The prevalence of peptic ulcer in the general population varies from 1.8%-4.3%.[17,18] Perforation occurs in about 7%.[10,11] In an earlier survey at this hospital,[12] 2.3% of patients had endoscopically confirmed ulcers. There is no data on the incidence and prevalence of acute abdomen in drug users. A total of 3023 drug users were seen at Al Amal Hospital, Jeddah between January and December 2000 (inclusive). Of these, 646 had heroin dependence, and three cases of acute abdomen were diagnosed in this period. This would give the overall incidence rate of acute abdomen in drug users of around 0.10% and among heroin users of 0.31%.

These case reports may be of importance to general surgeons, psychiatrists and ER physicians in drawing their attention to the possibility of drug use as a possible cause of acute abdomen.

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Filariasis: A Report of Three Cases

To the Editor: We read with interest the above study by Abdul Haleem.[1] The author mentioned that three cases were reported during a period of 20 years, yet the date of each case was not reported. The author mentioned that the Ministry of Health Central Laboratory shows a relatively higher incidence of filariasis. I would like to report that the Central Laboratory diagnosed only three cases of filariasis in the last seven years (1416-1422), and all were non-Saudis. It is clear that the reference to the 28 cases of 1964-1980 is outdated by the socioeconomic development that Saudi Arabia has enjoyed over the last 30 years.

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Reply

This is in response to Dr. Al-Mazrou's letter regarding the above-mentioned article. His first query was about the details of these patients and the dates when diagnosis were made. Since our paper was meant to highlight the diagnostic pitfalls in order not to miss the correct diagnosis, epidemiological information regarding these patients were considered irrelevant. However, Case 1 was a 68-year-old Saudi female who had a biopsy on 13 January 1994. She was originally from Jizan and was living in Riyadh at the time of the biopsy. Case 2 was a 78 year-old Saudi female, who was biopsied on 17 March 2001. Case 3 was a 32-year-old male who was biopsied at the Ministry of Health Central Hospital. We received the biopsy material for second opinion on 10 January 1984. Since he was not an RKH patient, we do not have the documents of his nationality, but was referred to us as a Saudi. The second query was about the mention of 28 cases between 1964 and 1980, which Dr. Al-Mazrou considered as outdated. The present incidence of filariasis (3 cases in 20 years) is low and is probably related to the improved socio-economic conditions. The fact, however, remains that 28 cases were seen in earlier days (1964-80) when expatriate population was very low and mostly included higher salaried professionals.

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Mood Disorders among Iranian Opioid-Dependent Patients

To the Editor: Substance dependents have high rates of depression.[1-3] The results of a research showed that success or failure in detoxification treatment of opioid-dependent outpatients was best predicted by initial psychiatric symptomatology.[2] Research evidence showed that co-existing psychiatric disorders, especially mood disorders can interfere with the course and treatment of substance dependents. In Iran, like many countries, substance use disorders have become a big problem. Iranian drug policy views substance abuse and dependence as criminal behavior and accordingly, a large number of opioid dependents are currently incarcerated in jails. In Iran, illegal substances include alcohol, opioids, cannabis, cocaine, LSD, amphetamines and other hallucinogens. Those substance dependents who seek treatment voluntarily are not arrested and could be treated. Very little is known about the rate of mood disorders in opioid dependents in the Iranian population, and our aim was to assess this phenomenom in Iran.

Subjects and Method

The data were gathered from 500 consecutive opioid dependents, using DSM-IV criteria for opioid dependence from private and government clinics (for treatment-seeking opioid dependents) in Shiraz city. Informed consent was taken, and subjects were assured of strict confidentiality. Subjects had been using opioids for a duration of at least 12 months.

They were interviewed at least three weeks after standard detoxification treatment for seven days. All interviewees were opioid-free for at least three weeks before the interview was carried out privately by a board-certified psychiatrist and using the DSM-IV criteria for mood disorders.

Results

The data were gathered from 500 (487 men and 13 women) unpaid opioid-dependent patients whose mean age was 33.37, ranging from 16 to 67 years. Table 1 shows age distribution of the subjects. As Table 2 shows, the majority 274 (54.8%) reported having substance-induced depression. Of the subjects, 319 (63.8%) reported use of opium of more than 5 years, and 181 (36.2%) reported use of between 1 to 5 years.

Discussion

A significant portion of opioid dependents in the community never reveal their condition and only a small number seeks treatment or any other psychiatric help voluntarily. Thus, the participants of the current research are not representative of the opioid dependents in Iran. In this study, 336 (67.2%) of the subjects were diagnosed as having mood disorders. The most prevalent type of mood disorders was substance-induced depression (54.8%), followed by major depression (7.4%) and dysthymia (2.8%). Bipolar mood disorder type I was rarely seen (0.6%), and none was diagnosed as bipolar mood disorder type II.

The high rates of mood disorders, especially substance induced depression, in this research suggests that depressed opioid dependents are highly motivated to seek treatment and are more likely to be identified and receive treatment.

Many studies have shown high rates of psychiatric disorders, especially mood disorders in opioid dependents.[4,5] Because of high rates of mood disorders in opioid-dependent patients, psychiatric services should be open and accessible to the patients, especially those who voluntarily seek help and treatment.

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A Proposed Role for Physicians in School Health

To the Editor: It has been estimated that more than half of the world's population is below the age of 25 years. At the end of the year 2001, there were 2 billion teenagers on the planet, more than there have ever been in the history of mankind.[1] In an era of increasing technological access and rapid innovation, the potential of this population is unbounded. However, if we fail to nurture their health, education, hopes and skills, their destabilizing effects on the political, social and economic systems could be immense.

Childrens' health has improved steadily over the past several decades. Children who in the past would have died in infancy are surviving into childhood, adolescence, and adulthood. However, the changing social, economic and political conditions both locally and globally, impose multiple threats and impairments to their physical, mental and social health.

The interaction between health and education has a major impact on the development and well-being of children. School achievement is affected by children's health, and health is affected by what children learn and do at school. Healthy habits can be taught in the classroom, modeled by teachers, and learned from peers. In addition, the child's health can be adversely affected by the negative physical and emotional environment of the school, and by the lack of nutritional and physical education programs.[2,3]

More children than ever before are attending schools, and for longer periods of their lives. Since the school years are a formative period in the child's development, the school is responsible for providing efficient means of improving the child's health, self esteem, behavior, and life skills (abilities related to effective decision-making, communication, understanding emotions, critical thinking, coping with stress, etc). Schools also provide a place where interventions of many specific diseases can efficiently and economically be implemented. Therefore, in every nation, schools could do more than perhaps any other single institution to improve the well-being and competence of the young generation. In addition, schools can also provide the setting to introduce health information to the community and, can lead the community by advocating policies and activities that promote health.[1]

The range of activities that fall under the rubic of schools health services requires the involvement of a variety of professionals, including school nurse, physician, dentist, counselor, psychologist, social worker and other pupil services personnel.[4] Although physician are trained to be clinicians, there are many good reasons for physicians, especially pediatricians and public health specialist, to be involved in school health. Working with schools extends the physician's influence within the community and allows him to affect school children and their families. Members of the community, including school staff, value the physician's work and view him as a consultant on health issues, particularly in his specialty. The aim of this article is to introduce the concept and scope of comprehensive or coordinated school health programs (CSHPs), propose different roles the physician can play to become involved in school health, and the skills physicians should acquire and the general principles they should follow to succesfully play these roles.

Components of School Health

For physicians to work positively in the school system, they should be aware of the difference between educational and healthcare systems. Each system has its own priorities, language, timeline, structure and hierarchy. In addition, they should have a wider and more comprehensive definition of health as "the complete physical, mental and social well-being and not merely the absence of disease or infirmity."[5]

The CSHP that effectively addresses student's health and improve their ability to learn consists of many components. Each component contributes in unique ways yet overlaps with other components. The definition and model of CHSPs can vary significantly in different educational healthcare systems, and no single one is best. Although the CSHPs must be developed according to the needs and resources of the community they serve, they should ideally include the following basic eight components.[6,7]

1. **Health education.** A planned program that addresses the physical, mental, emotional and social dimensions of health; develops health knowledge, attitudes and skills, and is tailored to each age level. It should be designed to motivate and assist students to maintain and improve their health, prevent disease, and reduce health-related risk behaviors.
2. **Healthy school environment,** including the physical, emotional and social climate of the school. It should be designed to provide safe, healthy and supportive environment that promote both health and learning.
3. **School health service,** including preventive services, early detection and intervention, emergency care, referral to health services, and management of acute and chronic health conditions. Such services should be designed to promote the health of the student, identify and prevent health problems and injuries, and ensure care for students.
4. **Nutrition service,** including nutritional education, provision of nutritious and appealing meals, and an environment that promotes healthy eating behavior for all children. Such services should be designed to maximize student's education and health potential for a lifetime.

5. **Physical education.** A planned sequential program that promote physical fitness and includes activities students can pursue throughout their lifetime. It should be designed to develop basic movement skills, sports skills, and physical fitness as well as to enhance mental, social and emotional abilities.
6. **School counseling psychological, and social services.** Activities that focus on cognitive, emotional, behavioral and social needs of individuals, group and families. Such services should be designed to prevent and address problems, facilitate positive learning and health behavior, and enhance healthy development.
7. **Health promotion for school staff** including health assessment, education and fitness activities for school staff. It should be designed to maintain and improve their health and well-being, allow them to demonstrate a commitment to health, and to serve as positive role models for students.
8. **Parent and community involvement in schools.** Partnership among schools, families, community and individuals. It should be designed to ensure wide range of resources and support that enhance the health and well-being of students and their families. However, educational and health professionals have begun to realize that successful health promotion through schools is not the result of the success of these components individually; it is a reflection of an organized, coherent approach to a wide range of health issues, implemented through comprehensive and holistic strategies.[1]

The Role of Physicians

Physicians can be a general resource to schools and school health programs. They can visit schools and donate time to play many specific roles, such as health educator or promoter, advisor, trainer, consultant, referral agent, recipient of referrals and communication link for parents and schools. Physicans also can play specific roles in health screening, development of health alerts or bulletins, collaborations in the community on issues affecting schools, and drafting, revising and evaluation of school programs.

Many physicians may not have been in a school since they were students themselves. They may become involved in the medical profession to the extent that they forget that the people they see and treat in their clinics and hospitals had passed through the educational channel, the school. Physicians need to reassess their attitude and practice in order to deal with the community health problems, and to participate in active health promotion of school children

There are seven skills physicians working with schools should develop. They can develop some or all of these skills depending on their needs and interests. For the physician beginning his interactions with school and school personnel, the skills are a "menu" from which to choose. These skills are:

1. Consulting schools on health issues.
2. Drafting and revising school health policies.
3. Consulting schools about health education.
4. Communicating health messages to school staff and students.
5. Assessing community health needs and determining services parameters.
6. Evaluating the effectiveness of school health programs. The physician should be able to observe, record and analyze data, and translate it into functional recommendations.
7. Serving in school advisory councils.

General Guidelines for Physicians Working with Schools

There are some general principles which physicians should follow when working with school health staff and school personnel. These principles are:

1. Setting up relationship with all levels and departments of education system.
2. Facilitating open communication through encouraging direct communication between schools and parents, attending a meeting at school if necessary to share information, and listening carefully to concerns and questions of the school personnel and respond to them.
3. Becoming aware of laws and regulations which affect the health of school children as well as the formal and informal decisions taken in schools that is related to health.
4. Respecting the interest and abilities of your colleagues, and approach all school personnel, respect the authority of the others, learn the rules of the school setting and understand the limits and abilities of others.
5. Recognizing and mobilize other potential health resources in the community, particularly human resources in other health specialties, such as nutrition, psychology, parasitology, etc., and use them approximately in promoting student's health.
6. Always keeping the background of different schools in mind, do not make demands which are very difficult for schools to meet, and do not expect many changes to quickly.

The Role of the Physician in Health Education

Health education is the cornerstone of health promotion. It plays an essential role as one of components of the CSHPs. Health education has been defined as "the lifelong process by which individuals acquire knowledge, attitudes and behavior that promote health and foster wise decision for solving personal, family and community health problems."[8,9] The key to effective health education lies in the teacher who delivers it. Unfortunately, many teachers have limited or no training in health education or in the methods for teaching the life skills students need to be engaged in health enhancing behaviors.

Physicians can help in the implementation and improvement of health education in schools. They can assess the needs in terms of which health risk behavior are prevalent; participate in revising and evaluation of school health education programs and curricula to determine if it is adequate; teach health related topics to school staff, and on special occasions to students and parents; and reinforce the messages taught in school with both students and their parents during clinical office visits. In school health education, the physicians should focus on:

1. Behavior and conditions that promote health or that put health at risk.
2. Knowledge, attitudes, beliefs, and life skills related to the development of healthy behavior and create health promoting conditions.
3. Providing learning experience that allow students and school staff to practice skills and model behavior.

The cooperation between schools, the health sector, and the community is necessary for school health to be effective and successful. This needs the utilization of all available resources, especially the physicians who are key resource persons and have great respect in their communities. The physicians need to show leadership in health promotion. They need to plan and perform their role as partners in school health promotion which is vital to improve community health.

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ANNOUNCEMENTS

FELLOWSHIPS AND TRAINING PROGRAMS

Pediatric Neurology Fellowship Program

King Faisal Specialist Hospital and Research Centre invites applicants for its Pediatric Neurology Fellowship Program. This is a 3-year-fellowship training program, with two years spent in Riyadh and one year abroad. Applicants must have successfully completed training in an accredited residency training program, and successfully passed the Pediatric Arab Board certifying exam or its equivalent. For further information, please contact Academic and Training Affairs, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-464-7272, ext. 31834; fax: (966) 1-442-7237.

Postgraduate Training Program in Anesthesiology

The Anesthesiology Department of King Faisal Specialist Hospital and Research Centre is pleased to invite applications for its postgraduate training program in Anesthesiology. The course will involve one year of training at KFSH&RC, and a four-year residency training period in North America. For further information, please contact: Academic and Training Affairs, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-442-7215; fax: (966) 1-442-7237.

Graduate Diploma in Medicine (Imaging)

The University of Sydney, Department of Radiology, is offering via the internet, a course designed for qualified medical practitioners from outside Australia who wish to obtain training in Diagnostic Radiology. It is recommended that students who enroll in this 4-year part-time course work in a training position in Diagnostic Radiology in their home country. Upon completion of the course, graduates would be expected to be able to complete the examination requirements for registration as a Diagnostic Radiologist in their home country. The course, offered in distance mode only, comprises 8 units, including introductory and advanced units in imaging anatomy, imaging technology, imaging diagnosis and imaging pathology. For further information, please contact: paulash@med.usyd.edu.au or janet.frommer@tch.anu.edu.au. Website: www.usyd.edu.au/su/radiology/MSHomePage.htm.

Saudi Society of Nephrology

It is announced for the information of all readers that the Saudi Society of Nephrology which was established in 2001, has been approved by the appropriate government authorities. The society is meant for all physicians who have interest in nephrology transplantation, immunology, urology, etc., in the Kingdom of Saudi Arabia. The goal of the Society is to improve the quality of communication between physicians with interest in nephrology, and thereby improve the treatment of renal patients in Saudi Arabia, through the exchange of ideas, symposia, training, etc. For further information, please contact Dr. Ahmed Hassan Mitwali, President, at (966) 1-461-4006; fax: (966) 1-461-0428; e-mail: saudisocietyofnephrology@hotmail.com. Website: www.ssn-sa.com.

SYMPOSIA, MEETINGS AND CONFERENCES

Symposia and Workshops at KFSH&RC for 2003

The Department of Academic and Training Affairs of King Faisal Specialist Hospital and Research Centre (KFSH&RC) wishes to announce the forthcoming symposia and workshops at KFSH&RC: Introduction to Protemics, 3 May 2003 (2 Rabi Al Awal 1424); Health Promotion and Disease Prevention in Nursing, 13-14 May 2003 (12-13 Rabi Al Awal 1424); Evidence-Based Medical Practice, 28-29 May 2003 (27-28 Rabi Al Awal 1424); Muscular Dystrophy and Related Conditions, 29 September – 1 October 2003 (3-5 Shaban 1424); Electrophysiology in Adult and Pediatric Patients: A New Frontier, 7-8 October 2003 (11-12 Shaban 1424); Diabetic Foot Symposium, 14-15 October 2003 (18-19 Shaban 1424); Update in Diagnostic Imaging Symposium, 20-22 October 2003 (24-26 Shaban 1424); Spatial and Temporal Clustering of Disease and Risk Assessment in Public Health, 9-10 December 2003 (15-16 Shawwal 1424); Update in Pediatric Nephrology, 28-29 May 2003 (22-23 Shawwal 1424). For more information, please contact: Academic and Training Affairs, KFSH&RC, MBC 36, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-442-7238; fax: (966) 1-442-4153, (966) 1-442-4153; e-mail: web_symposia@ kfshrc.edu.sa. Website: www. kfshrc.edu. sa/symposia.

4th Medicine Essentials Workshop (Update on Common Clinical Problems and Practical Skills)

The Department of Family and Community Medicine in collaboration with the Continuing Medical Education, Medical Education Center, College of Medicine, King Saud University, Riyadh, is organizing the above workshop which will be held at the Towaiq Palace, Diplomatic Quarters on 4-7 May 2003 (3-6 Rabi Al Awal 1424). The Workshop is recognized by the Saudi Council for Health Specialties as 21 CME credit hours. For more information, please contact Dr. Khalid Kalantan, Chairman of the Organizing Committee, Department of Family and Community Medicine, Medical Education Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia. Tel: (01) 467-1551/1554/1556/2454; fax: (01) 481-1853;

e-mail: kkalantan@ ksu.edu.sa or cmecora@ksu.edu.sa. Website: www.mecksu.org.

The 29th Munich Endourological Symposium with Nursing Staff Seminar

The Department of Urology of the Technische Universitat Munchen, in Munich, Germany, wishes to announce that the 31st Munich Endourological Symposium with Nursing Staff Seminar will be held on 9-10 October 2003 (13-14 Shaban 1424). The Chairman of the Congress will be Prof. Dr. R. Hartung. For further information, please contact the Congress Secretary at Tel: 89-41-40-25-07; fax: 89-41-40-25-85; e-mail: mriu@lrz.tu-muenchen-de. Web address: www.mriu.de.kongress.

The 2nd International Consultation on Erectile and Sexual Dysfunction

The International Consultation on Urological Diseases (ICUD, the International Society of Urology (SIU), and the International Society for Sexual and Impotence Research (ISSR), in collaboration with the World Health Organization will be conducting the 2nd International Consultation on Erectile and Sexual Dysfunction on 28 June - 1 July 2003 (28 J. Awal - 1 J. Thani 1424) at the Palais des Congrès, Port Maillot, France. For further information, please contact Prof. Saad Khoury, Clinique Urologique, Hôpital de la Pitié, 83 bd de l'Hôpital, 75634, Paris Cedex 13, France. Tel: +33 1 17 71 20/21; fax; 33-1-42-17-71-42; e-mail: consulturo@aol.com or to Prof. Tom F. Lue, Professor and Vice-Chairman, Dept of Urology, UCSF, 400 Parnassus Avenue, a-633, San Francisco, CA 94143-0738, USA. Tel: +1-415-476-1611; fax: +1-415-476-884; e-mail: tlue@urol.ucsf.edu.

The 3rd International Nurse Practitioner Conference 2004: Critical Pathways in a Global Context

The Groningen University of the Netherlands in collaboration with the National Nurses Organization is pleased to announce the 3rd International Nurse Practitioner/Advanced Practice Nursing Network Conference to be held at the University on 29 June - 2 July 2004. The goal of the conference is to enhance and develop the role of the Nurse Practitioner (NP) and the Advanced Nurse Practitioner (ANP). This will be accomplished through critical debate on relevant issues, networking, small group discussions and idea sharing on many national and international issues facing nurses in general. The conference themes are Research, Professional Practice, Education and Leadership, Management and Policy. All topics will be related to the role of NP/ANP with special attention to critical pathways and care processes for specific populations. Interested participants are required to submit abstracts (not exceeding 250 words) for the conference, and should be received no later than 23 September 2003. For further information, please contact Ineke van Est, Conference Secretary, Faculty of Management & Organization, Groningen University, P.O. Box 800, 9700 Groningen, The Netherlands. Tel: (33) 50 363 3458; e-mail: I.van.Est@bdk.rug.nl. Website:www.anp2004.nl.

15th Scientific Session , Saudi Heart Association

The 15th Scientific Session of the Saudi Heart Association will be held in Jeddah, Saudi Arabia on 6-8 January 2004 (14-16 Dhu Al Qada 1424). The conference, organized by the Saudi Heart Association, will discuss recent issues and updates on cardiovascular medicine. Participating in the conference are distinguished international speakers.

Cardiovascular experts from Saudi Arabia will also be presenting papers on their latest findings in cardiovascular medicine. Major suppliers of cardiac products and equipment will be present to demonstrate their products to all attendees.

All physicians, researchers, technicians, nurses and others involved in cardiovascular medicine are invited to attend. The organizing committee invites colleagues to submit abstracts for presentation. Original work related to all aspects of cardiovascular diseases will be considered. The deadline for abstract submission will be on the 15th of September 2003.

For further information, please contact the Saudi Heart Association's Office, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel. 01-467-1434; Fax 01-467-2553, email: saudhass@ksu.edu.sa.

NEWS RELEASES

Philadelphia International Medicine Signs Marketing Agreement with China Trade Center

Philadelphia International Medicine (PIM) and The China Trade Center of Philadelphia (CTCP) have signed an agreement to market PIM healthcare education and training services in China.

The agreement allows for CTCP to contact government officials, medical schools and prominent hospitals and physicians in China to promote PIM services, such as training programs for health care administrators, advanced clinical programs for physicians, training programs for nurses, observerships and visiting physician programs.

"This agreement will expand the capabilities of PIM to bring its healthcare training programs and services to

China, which is investing heavily in medical services development and management. It presents a good partnership for both organizations as they collaborate to export Philadelphia's considerable healthcare expertise worldwide," said Andrew Wigglesworth, PIM president and chief executive officer.

The China Trade Center will use its contacts with officials in China to introduce PIM and its network of hospital and physicians. PIM will customize training programs based on the specific needs of the client , and the Trade Center will help to finalize negotiations and travel and accommodation arrangements.

"We are very excited to spread the word about Philadelphia's healthcare story throughout China," said KeKe Wang, president of the China Trade Center. "In China, there is a growing need for medical and health care training, and Philadelphia and its medical schools, business schools and nursing schools, together with its hospitals, is uniquely prepared to fill the need."

PIM was created by nine hospitals to establish the Philadelphia region as an international healthcare destination of choice. Its network includes The Children's Hospital of Philadelphia, Crozer-Keystone Health System, Fox Chase Cancer Center, Magee Rehabilitation Hospital, MossRehab Hospital, Pennsylvania Hospital, Temple University Hospital, Thomas Jefferson University Hospital and the University of Pennsylvania Medical Center.

Winner of 50 International Awards Named Director of Jefferson Liver Transplant Program

Renowned transplant surgeon Ignazio R. Marino, MD, who has personally performed more than 650 liver transplants, has been named director of Liver Transplant and Liver Surgery in the Division of Transplantation at Thomas Jefferson University Hospital, a member of the Philadelphia International Medicine (PIM).

"PIM and Thomas Jefferson University Hospital are very proud that Dr. Marino has brought his international practice here to Philadelphia," said Andrew Wigglesworth. "The hospitals and physicians of PIM include some of the best in the world, and we look forward to introducing Dr. Marino to our international patients and clients."

Dr. Marino has also been appointed associate director of the transplantation division and professor of surgery, Jefferson Medical College of Thomas Jefferson University. Dr. Marino recently came to Jefferson from the University of Pittsburgh Medical Center and from Palermo, Italy, where he served as director of the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (a partnership between the University of Pittsburgh Medical Center and the Italian National Government).

Dr. Marino most recently served as professor of surgery at the School of Medicine, University of Pittsburgh, and the Schools of Medicine of the Universities of Perugia, Milan, and Palermo, Italy.

Board certified in general and vascular surgery, Dr. Marino was assistant professor of Surgery from 1983 to 1990 in the department of Surgery of the Catholic University of Rome, Italy, during which time he spent four years training in two most prestigious transplant centers in the world – the Transplant Center of the University of Cambridge, directed by Prof. Sir Roy Y. Calne, and the Pittsburgh Transplantation Institute, directed by Dr. Thomas E. Starzl.

Advanced Radiation Technique Minimizes Side Effects in Breast Cancer Treatment

Fox Chase Cancer Center is now offering the most precise radiation therapy currently available for treating women with breast cancer. It's called intensity-modulated radiation therapy, or IMRT.

Radiation therapy is a must after breast conserving surgery to decrease the risk of the cancer recurring. However, it is common for a woman who needs radiation to be concerned about the possible long-term effects of radiation to her skin, lungs and heart after traditional radiation therapy. IMRT is a technological advance that improves the delivery of radiation for breast cancer while minimizing the side effects.

IMRT can be optimally designed to deliver radiation to the breast while sparing surrounding healthy tissue and organs with a precision not possible with traditional radiation. IMRT works by allowing the radiation beams to vary in intensity. IMRT equipment divides each beam into multiple, smaller, more focused, pencil-thin beams that can precisely target the tumor.

"Traditional radiation therapy often causes skin irritation during treatment, and may result in long-term swelling, redness or hardening of the treated breast," says Gary Freedman, MMD, a radiation oncologist at Fox Chase. "In some cases, the lung and parts of the heart and coronary arteries can be exposed to radiation. With the precise technology offered by IMRT, these side effects of conventional radiation are minimized by avoiding or reducing the radiation dose to these sensitive areas."

Another benefit of IMRT is that radiation oncologists are able to shorten the treatment time for patients. "Traditionally, women undergo radiation treatment every weekdays for seven weeks. With IMRT, we are developing ways to shorten that treatment to five weeks, which is a huge advance when it comes to the patient's quality of life," Freedman explains.

Fox Chase Cancer Center physicians have hundred of hours of experience with IMRT, which is routinely used to treat men with prostrate cancer at Fox Chase. Fox Chase Cancer Center, one of the nation's first comprehensive cancer centers designated by the National Cancer Institute in 1974, conducts basic and clinical research; programs of prevention, detection and treatment of cancer; and community outreach.

PIM establishes Second-Opinion Program with Chowgule Mediconsult Private Limited

Philadelphia International Medicine (PIM) and Chowgule Mediconsult Private Limited (CMPL) have jointly established a medical second-opinion program that will provide benefits to patients in India as well as the Philadelphia medical community.

Through the program, physicians at hospitals within the PIM network will review medical records and provide treatment alternatives to patients in India accessing the program through centers established by CMPL.

"This second-opinion program brings together the medical community of Philadelphia, regarded as among the best in the world, with a patient population eager to access our medical expertise," said Leonard Karp, executive vice president and chief operating officer of PIM. "In our efforts to build recognition and opportunity in India, we are very fortunate to partner with Dr. Chowgule and the Chowgule Group.."

CMPL, headed by Rohini V. Chowgule, MD, managing director, has the backing of the Chowgule Group, one of India's largest business houses. It has an office in Mumbai with plans to expand to three additional centers – Panaji (GOA), Bangalore and Chennair (Tamil Nadu) where the Chowgule family already has business operations. Other offices are planned for New Delhi, West Bengal, Pune, Jamnagar and Veraval.

"The new contract with PIM will help CMPL to bring an affordable, high quality second-opinion program to the people of Mumbai. We are very pleased to join with such renowned hospitals and physicians as the Philadelphia, regarded as among the best in the world, with a patient population eager to access our medical expertise," said Leonard Karp, executive vice president and chief operating officer of PIM. "In our efforts to build recognition and opportunity in India, we are very fortunate to partner with Dr. Chowgule and the Chowgule Group."

Through the arrangement, medical reports will be posted to secure Internet sites and will be made available to selected PIM physicians to review. The system can accommodate X-rays, MRI and CT scans, as well as other images.

The agreement also provides for easy access to PIM's hospital network in Philadelphia for patients who choose to come to the United States for their care. Patients will receive through PIM a full range of support services to assist them while in the United States.

The Children's Hospital of Philadelphia Again Ranked Number One in the U.S.

Child magazine has again ranked The Children's Hospital of Philadelphia the best children's hospital in the United States. This is the second consecutive time Child magazine has ranked Children's Hospital "number one." The Children's Hospital of Philadelphia is a member of Philadelphia International Medicine (PIM). To make a medical appointment at Children's Hospital, call PIM at 215-735-3575.

"We are exceptionally proud of the commitment to excellence that is demonstrated by its number one ranking," said Andrew Wigglesworth, president and CEO of PIM. "Children's Hospital and all the hospitals of the Philadelphia International Medicine network represent an extraordinary medical resource for physicians and patients."

Child magazine also ranked The Children's Hospital of Philadelphia's cardiac and oncology centers as the best in the nation and the Newborn/Infant Center ranked second highest in the nation.

The Child magazine survey is based on hard data rather than subjective opinions. It is the result of a comprehensive data-based study of children's hospitals across the United States. The study looked at depth and breadth of clinical outcomes, research activities, various support services provided to children and families, and the amount of government research funding hospitals receive.

The Cardiac Center at The Children's Hospital of Philadelphia is an established provider of multidisciplinary care for children with acquired and congenital heart diseases and houses an internationally renowned program in cardiothoracic surgery, as well as the East Coast's largest heart and hear/lung transplantation program. The Cardiac Center performs more than 900 cardiac surgical procedures a year, including 500 pediatric open heart surgeries, and provides cardiac evaluation and treatment in more than 17,000 outpatient visits annually.

The Center's extensive experience in cardiac catheterization techniques has helped foster its expansion from solely a diagnostic tool to its use as a therapeutic modality. Cardiac Center surgeons are leaders in the use of pioneering techniques for minimally invasive cardiac surgery in children, including the modification of instruments for use in pediatric patients. The Fetal Heart Program, a subspecialty within the Cardiac Center, provides earlier diagnoses that lead to earlier treatment interventions and improved outcomes overall. It specializes in the detection, evaluation and ongoing management of congenital heart disease. It performs more than 1,200 fetal echocardiography studies annually, making it among the largest programs of its kind in the nation.

The Oncology Program at The Children's Hospital of Philadelphia is one of the nation's largest cancer programs exclusively dedicated to children, and is home to an international center for pediatric cancer research. The institution's oncology unit consists of 31 inpatient beds including a bone marrow transplant unit and a dedicated outpatient oncology clinic. The Oncology Program admits 400 new cancer patients each year, and provides follow-up care to an additional 3,600 children. Researchers in the Oncology Program are leading the way in classifying and treating neuroblastoma, the most common solid tumor in children, and is at the forefront of developing new therapies to treat pediatric brain tumors.

Additionally, researchers here have pioneered a study of the long-term effects of treatment on survivors of childhood cancer, and developed the first long-term follow-up program in the nation for childhood cancer survivors.

The 50-bed Newborn/Infant Center (NIC) is equipped to provide for the complete range of neonatal and infant critical illnesses including all types of respiratory, surgical, cardiac, genetic, renal, neurological, hematological and metabolic diseases. The NIC receives approximately 900 admissions per year and serves as a primary referral center for other neonatal intensive care units. Infants with certain problems, such as those with severe lung disease or surgical abnormalities identified prenatally, are frequently referred on both the national and international level to the NIC for highly specialized care.

The Center for Fetal Diagnosis and Treatment established in 1995 is one of only two comprehensive centers worldwide to offer technologically advanced, multidisciplinary care for unborn babies with genetic or anatomical abnormalities and collaborates with the NIC team to provide optimal continuum of care for these newborns post-partum.

Philadelphia International Medicine is an organization that provides medical and patient support services to international patients. It also provides continuing medical education and health care training and education to international physicians, administrators and other practitioners. As the international department of several Philadelphia-area hospitals, international patients gain access to physicans and hospitals rated among the best in the world through one telephone call to PIM. You can reach PIM by calling 1-215-735-3575; fax, 1-215-790-1267; or email, physicans@philadelphiamedicine.com. You can find out more about PIM through its Website at www.philadelphiamedicine.com.

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مقارنة بين استئصال الكظر عن طريق تنظير البطن وفتح البطن: تجربة في مستشفى الملك فيصل التخصصي ومركز الأبحاث، الرياض

الخلفية : إن استئصال الكظر عن طريق تنظير البطن أمر مقبول حالياً وهو أفضل من طريقة فتح البطن. نصف هنا تجربتنا في استئصال الكظر ونقارن النتائج لكل من طريقة فتح البطن وطريقة التنظير.

المرضى والطرق: لقد قمنا بإجراء ٢٣ عملية استئصال للكظر خلال الفترة من مارس ١٩٩٩م حتى مارس ٢٠٠٢م. وتم إجراء العملية من الجهة الأمامية للبطن بالنسبة لطريقة فتح البطن، ومن الجهة الجانبية لطريقة التنظير. وتم تحليل بيانات المجموعتين ومقارنتها.

النتائج: لا يوجد فرق في حجم الورم أو تشريحه المرضي بين المجموعتين. كان حجم الورم أصغر، ومدة العملية أطول وكمية الدم المفقودة أقل في المجموعة التي أجريت لها العملية بالتنظير. إلا أن هذه الإختلافات غير ذات أهمية من الناحية الإحصائية. كان متوسط الاقامة بالمستشفى أقل (٥,١ مقابل ٩,٢ يوم، P<٠,٠١)، وكان متوسط استخدام مسكنات الألم المخدرة بعد العملية أقل (٤,٢ مقابل ٨,١ حقنة، P<٠,٠٥)، وكان متوسط الوقت بالنسبة لاستئناف التغذية عبر الفم اسرع (١,١٧ مقابل يومين، P<٠,٠١) في مجموعة التنظير عند مقارنتها بمجموعة فتح البطن.

الخاتمة: إن استئصال الكظر عن طريق تنظير البطن إجراء آمن ويمكن اجراؤه لأغلب أمراض الكظر. وتعتبر فترة الشفاء بعد العملية أسرع، كما أن الألم التالي للعملية أقل، وفترة الإقامة بالمستشفى أقل.

المدونات الطبية السعودية ٢٠٠٣،٢٣ (١-٢): ٣٦-٣٨

تصحيح

ظهر اسم الدكتور محمد زهير القاوي محرر النصوص العربية في المدونات الطبية السعودية مع اسم كل من الدكتور عبد الرحمن الراجحي و الدكتور عبدالله العريفي في النص العربي لمقالتي كلية الأطباء الأمريكية في العدد السابق (العدد ٥-٦ ، المجلد ٢٢ ، ٢٠٠٢، ص ٤٢٦-٤٥٠) ، وبما أن الدكتور القاوي هو محرر النصوص العربية للمدونات الطبية السعودية و لم يكن ضمن من تم منحه حقوق النقل والترجمة من قبل كلية الأطباء الأمريكية فإننا نصحح ذلك هنا لكل من الدكتور الراجحي و الدكتور العريفي والقراء ، كما نشكر الدكتور القاوي على مساهمته التحريرية ، ولذا لزم التنويه.

المحرر

الدم(P<0.01) والحماض الاستقلابي المتأخر للخداج (P<0.01) والإنتان المثبت بالزرع (P<0.05). غير انه لم يكن هناك فرق مهم بين المجموعتين من حيث حدوث الالتهاب المعوي القولوني الناخر (P<0.05).

الاستنتاج: تدعيم الحليب البشري له تأثيرات مفيدة على نمو الرضع ذوي الأوزان المنخفضة جدا حين الولادة، فهو يقلل مدة الإقامة في المستشفى والمضاعفات المرتبطة بالخداج ووزن الولادة المنخفض جدا، مع ما لذلك من فوائد اقتصادية ونفسية على الوالدين.

المدونات الطبية السعودية ٢٣،٢٠٠٣ (١-٢): ٢٨-٣١

تفتيت الحصى الموضعي بموجة صدمية خارج الجسم، كعلاج أولي لحالات تحصي الحالبين

خلفية: الهدف من هذه الدراسة هو تقييم نتائج تفتيت الحصى بموجة صدمية خارج الجسم بوصفها طريقة علاجية أولية لتحصي الحالبين على مختلف المستويات.

المواد والطرق: تم علاج ١٦٦ مريضاً متتالين، مصابين بحصوات حالبية منعزلة (٧٣ في أعلى الحالب، ٤ في منطقة الوسط، ٨٩ في أسفله) بطرق التفتيت الموضعي بالموجات الصدمية خارج الجسم، وفي العيادة الخارجية أي دون الحاجة للتنويم. وقبل اللجوء إلى إجراء التنظير الحالبي كعلاج بديل، فلقد أعطي كل مريض فرصة ثلاث جلسات علاجية كحد أقصى. هذا وتم حساب معدل النجاح وفقاً للاختفاء الكامل للحصيّات واختفاء أي انسدادات مصاحبة. كما تم تسجيل معدلات إعادة العلاج، والمضاعفات، والوقت المستغرق للقضاء على الحصيات بصورة تامة.

النتائج: تحقق لـ ١٥٢ مريضاً اختفاء كاملاً للحصيات (٩١،٦%) بعد مرور عشرة أيام في المتوسط (النطاق ما بين ١-٢٨). كما كان متوسط معدل العلاج ١،٣ جلسات لكل مريض. وكمجموعات مكتملة، فإن المصابين بحصلت في أسفل الحالب تطلبت حالاتهم جلسات علاجية أكثر من أولئك المصابين بحصيات في أعلى الحالب، وكان الفرق هاماً من ناحية إحصائية. إلا أن هذه الفروق لم تكن ذات قيمة إحصائية فيما يختص بمعدلات النجاح النهائي، والوقت المستغرق لاختفاء الحصيات. وعند المطابقة تبعاً للحجم، يصبح معدل النجاح هو الأكثر انخفاضاً بالنسبة لحصيات أسفل الحالب والتي يتجاوز قطرها (١) سم.

الخلاصة: نرى أن طريقة تفتيت الحصى بموجة صدمية خارج الجسم هي خيار علاجي آمن وغير باضع للقضاء على معظم حالات تحصي الحالبين بمستوياتها المختلفة. إذ يمثل تنظير الحالبين خياراً علاجياً بديلاً في حالة فشل طريقة تفتيت الحصى بموجة صدمية (SWL)، أو في حالات علاج حصيات أكبر حجماً في أسفل الحالب حينما يمكن أن يصبح الخيار العلاجي الأول.

المدونات الطبية السعودية ٢٣،٢٠٠٣ (١-٢): ٣٢-٣٥

ومفرطي وزن وبدينين. تم تسجيل ما مجموعه ١١٧ بديناً (م ك ج > ٣٠ (كغم/م^{٢})، و ١٨٥ مفرطي وزن (م ك ج = ٢٥-٢٩,٩ (كغم/م^{٢}) و ١٥٥ من ذوي الأوزان العادية (م ك ج < (كغم/م^{٢})، تم استخدام ردة فعل سلسلة البوليميراز والرحلان الكهربائي لدراسة تعدد أشكال النمط الجيني. وتم الحصول على ١٩٠ للنمط خ (خبن) و ٤٩٠ للنمط غ (غرز) في نسبة ٢% من الرحلان الكهربائي.

النتائج: كان توتر النمط الجيني خ خ بنسبة ٧٦,٩% في البدينين، و ٧٣,٥% في مفرطي الوزن، مقارنة بـ ١٩,٦٦% أ ب د ٢٤,٨٦% للنمط الجيني (خ غ) في البدينين ومفرطي الوزن على التوالي. بين ذوي الأوزان العادية، كان التوتر متدنيا بصورة ملحوظة للنمط الجيني خ خ ومرتفعاً للنمط الجيني (خ غ). ومثالاً لذلك ٥٨,٧% لـ خ خ و ٤٠% لـ (خ غ). كان تواتر الأليل في البدينين ٠,٨٦٧ و ٠,١٣٣ لـ خ وغ على التوالي. بينما كان التواتر في مفرطي الوزن ٠,٨٥٩ و ٠,١٤١ على التوالي مقارنة بـ ٠,٧٨٧ و ٠,٢١٣ في ذوي الأوزان العادية.

الخاتمة: إن النمط الجيني خ خ والحليل يحدثان بمعدلات عالية في مفرطي الوزن والبدينين السعوديين، وربما يكون لهما دور في تراكم الشحوم بالتأثير على المسارات الاستقلابية للشحوم، مما يؤدي بالتالي إلى الإصابة بفرط الوزن والبدانة.
المدونات الطبية السعودية ٢٠٠٣،٢٣ (١-٢): ٢٤-٢٧

تأثيرات تدعيم الحليب البشري على عوامل المراضة لدى الرضع ذوي الأوزان المنخفضة جدا حين الولادة

مقدمة: أصبح موضوع استعمال الحليب البشري مصدرا وحيدا للعناصر الغذائية للرضع المولودين قبل الأوان موضع جدل في السنوات الأخيرة. لذا درسنا عوامل المراضة المرتبطة بتنويم الرضع الذين كانت أوزانهم منخفضة جدا حين الولادة والذين تغذوا على حليب بشري مدعم وغير مدعم.

المرضى الطرق: تم توزيع مائة رضيع من ذوي الأوزان المنخفضة جدا حين الولادة بصورة عشوائية على مجموعتين مع المطابقة بالنسبة لفترة الحمل والوزن. المجموعة الضابطة (عددها ٥٠، متوسط وزن الولادة ١٢٣٩± ١٨٦ غم، متوسط فترة الحمل ٢٩,٣ ± ٢,١ أسبوع) تغذت على الحليب البشري فقط. ومجموعة التدعيم (عددها ٥٠، متوسط وزن الولادة ١٢٤٥±١٩١ غم، متوسط فترة الحمل ٢٩,٥±٢,١ أسبوع) تغذت على الحليب البشري المدعم من المسلك الهضمي بعد أن وصل الرضع إلى حجم ١٤٠ مل/كغم/ يوم. تم قياس الوزن مرتين في الأسبوع، والحصول على المناسب الكيميائية الحيوية للوضع الغذائي وحالة العظم وكهارل المصل مرة واحدة في الأسبوع، وتقييم الأدلة السريرية على الإنتان والالتهاب المعوي القولوني الناخر والعجز عن احتمال التغذية بصفة منتظمة إلى أن تم إخراج الرضع من المستشفى.

النتائج: كانت مدة التنويم في المستشفى أقل من ٤٥ يوما لدى غالبية (٩٤%) الرضع من مجموعة التدعيم في حين أن غالبية (٦٦%) الرضع من المجموعة الضابطة بقوا في المستشفى أكثر من ٤٥ يوما ($P<0.01$). شوهد انخفاض فسفور المصل وارتفاع الفسفاتاز القلوي بدرجة أكثر تواترا لدى المجموعة الضابطة ($P<0.01$)، وكذلك نقص صوديوم

الاستنتاج: إن نسب وقوع هذه الاضطرابات لدى هذا الجزء من الجمهور اللبناني يستوجب التفكير في تطبيق برنامج وطني شامل لتقصي المواليد.

المدونات الطبية السعودية ٢٣،٢٠٠٣ (١-٢): ١٦-١٩

مستويات الفلوريد في مياه الشرب في المنطقة الوسطى في المملكة العربية السعودية

الخلفية: تم تصميم هذه الدراسة لتقييم مستويات الفلوريد في مياه الشرب في المنطقة الوسطى في المملكة العربية السعودية.

المواد والطرق: تم تجميع ٨١٧ عينة من المياه من ٢٦٠ موقعاً في المنطقة الوسطى من المملكة العربية السعودية. تم استخدام جهاز المقياس الطيفي للإمتصاص الذري في تحليل عينات المياه لتحديد مستويات الفلوريد.

النتائج: أظهرت النتائج أن مستويات الفلوريد تراوحت بين ٠,٠٠ و ٦,٢٠ جزء في المليون. كانت نسبة ٧٥% و ٥٦% من سكان الرياض والقصيم على التوالي تتناول نسبة متدنية جداً من الفلوريد (٠,٠٠-٠,٣٠ ب ب) بينما كانت نسبة ٣% من السكان في كلتا المنطقتين تتناول مستويات من الفلوريد تتراوح ما بين ٠,٦١ إلى ٠,٨٠ جزء في المليون. كانت توجد نسبة عالية من سكان القصيم أكثر من سكان الرياض تتناول مستويات أعلى من الفلوريد (<٠,٨١ جزء في المليون) حيث بلغت نسبة ٢٨,٦٣% في القصيم ونسبة ٩,٤٤% في الرياض.

الخلاصة: يمكن الاستفادة من نتائج هذه الدراسة كقاعدة بيانات أساسية لمستويات الفلوريد في مياه الشرب والبرامج الأخرى للوقاية من أمراض الأسنان في المنطقة.

المدونات الطبية السعودية ٢٣،٢٠٠٣ (١-٢): ٢٠-٢٣

التواتر المتزايد في الإنزيم المحول للأنجيوتنسين والنمط الجيني خ.خ. في المرضى السعوديين البدينين ومفرطي الوزن

الخلفية : أجريت دراسات كثيرة لدراسة تعدد أشكال النمط الجيني للإنزيم المحول للأنجيوتنسين في الأفراد البدينين وذوي الأوزان العادية، وغالباً ما كانت النتائج متعارضة لدى مجموعات سكانية مختلفة. تشير بعض الدراسات إلى أن النمط الجيني مزدوج الخبن (خ خ) يحدث بمعدلات عالية في البدانة، في حين أن دراسات أخرى لم تشر إلى وجود ترابط بينهما. بما أن البدانة وإفراط الوزن يحدثان بمعدلات عالية بين السكان السعوديين فقد قمنا بهذه الدراسة لدراسة تعدد أشكال النمط الجيني للإنزيم المحول للأنجيوتنسين في الأفراد البدينين وذوي الأوزان العادية.

الأشخاص والطرق: شملت الدراسة ٤٥٧ فرداً من الذكور والإناث السعوديين تم قياس الطول والوزن واحتساب منسب كتلة الجسم. وبالاعتماد على قيمة منسب كتلة الجسم(م ك ج) تم تصنيف إجمالي جمهور الدراسة كعاديين،

التحولات النسيجية والتحولات الكيميائية النسيجية في الكلية المسببة بالرصاص

الخلفية: بالرغم من أن التسمم بالرصاص هو أحد أكثر أنواع التسمم المعدني شيوعاً إلا أن التحولات الكيميائية النسيجية في أنسجة الكلى الناتجة عن التعرض المزمن للرصاص محدودة و لم يتم التعرف عليها جيداً.

المرضى والطرق: تم تعريض ٦٠ جرذ ذكر أبهق إلى ترايهادريت أسيتات الرصاص (٠,٠، ٠,٢٥، ٠,٥، ١,٠ و ٢٪ لمدة ١-١٢ شهر) عن طريق مياه الشرب لتقصي التحولات النسيجية والتحولات الكيميائية النسيجية التي تطرأ على أنسجة الكلى بسبب الرصاص.

النتائج: إن التعرض المزمن للجرعات السامة من الرصاص أدى إلى تلف أنبوبي متزايد وتلف كبيبي وتلف خلالي. حدثت التحولات الأنبوبية قبل الكبيبية والخلالية، وشملت تفاوت النوى، وتغلظ خلوي نووي، وتضخم النواة، واندماجات داخل النواة وسيتوبلازمية مع توسع أنبوبي، ونخر، وتفجّ، وفرط تنسج أنبوبي وورم غدي أنبوبي صلب. أما التحولات الكبيبية فكانت فرط الخلوية، وتشعب قطعي، والتهاب كبيبي تصلبي قطعي وبؤري، وتنكس زجاجي كبيبي وتحولات كبيبية.

الخاتمة: تشير النتائج إلى أن الرصاص يسبب تغيرات نسيجية وتغيرات كيميائية نسيجية في الكلية مما يؤدي إلى مضاعفات خطيرة.

المدونات الطبية السعودية ٢٠٠٣، ٢٣ (١-٢): ١٠-١٥

تقصي الاضطرابات الشائعة لدى المواليد في لبنان نتائج خمس سنوات من الخبرة

مقدمة: إن برامج تقصي الاضطرابات الشائعة مثل بيلة الفنيل كيتون وقصور الدرقية الخلقي وعوز الإنظيم G6PD لدى المواليد غير مطبقة بالكامل على المستوى الوطني في لبنان. لذا أجريت هذه الدراسة لتقصي الاضطرابات المذكورة آنفاً لدى مواليد المركز الطبي التابع للجامعة الأمريكية في بيروت على مدى ٥ سنوات.

المرضى والطرق: أخذت عينات دم بعد ٢-٣ أيام من الولادة ووضعت على بطاقات تقصي المواليد، وتم تقصي ما مجموعه ٩١١٧ مولودا باستخدام قياسات نشاط الفنيل ألانين والهرمون المنبه للدرقية والإنظيم G6PD على بقع الدم.

النتائج: اكتشفنا حالة واحدة لبيلة الفنيل كيتون وحالة أخرى لارتفاع الفنيل ألانين في الدم. اكتشفنا أيضا ٥ حالات لقصور الدرقية الخلقي الدائم، وبذلك تكون نسبة الوقوع ١:١٨٢٣. بدأ العلاج الهرموني التعويضي في السن ٩-٤٦ يوما. كانت نسبة الوقوع الإجمالي لعوز الإنظيم G6PD ١٠٦:٩١١٧ (١:٨٦ أو ١,١٦٪)، منها ٨٤ حالة عوز تام (١:١٠٩ أو٠,٩٢٪) و٢٢ حالة عوز متوسط.

تمام ووثوق سجل السرطان لدى مستشفى إحالة حكومي كبير بالمملكة العربية السعودية

الخلفية : أظهر السجل الوطني للسرطان عام ١٩٩٤م، وهو سجل مبني على السكان، أن معدل الوقوع الخام ٣٩/١٠٠ ٠٠٠ لجميع حالات السرطان في المجتمع السعودي. يشير هذا المعدل الخام المتدني إلى احتمال إغفال التبليغ عن بعض الحالات خاصة خلال السنوات الأولى.

الغرض من هذه الدراسة هو تقدير عدد الحالات المفقودة بسبب عدم التبليغ عنها، وتقييم صحة البيانات التي أبلغ عنها مستشفى إحالة حكومي كبير بمدينة الرياض.

المرضى والطرق: أجرينا مقارنة بين حالات السرطان، استقيناها من ثلاثة مصادر للبيانات: السجلات الطبية؛ وهي المصدر الأصلي لحالات السجل الوطني للسرطان، وتقارير التشريح المرضي، وشهادات الوفاة. تم تقدير حالات السرطان المفقودة باستخدام طريقة الالتقاط وإعادة الالتقاط باستخدام النموذج اللوغارتمي — الخطي من برنامج فاينرج Finberg لتصحيح الترابط فيما بين المصادر الثلاثة. قمنا بإعادة استخلاص الملفات لنحو ٨% (٣٩/٤٧٦) من الحالات المبلغ عنها سابقاً من نفس المستشفى لتقييم صحة البيانات.

النتائج: أبلغ عن إجمالي ٨١١ حالة سرطان عبر المصادر الثلاثة: السجلات الطبية ٦١١ (٧٥,٣%)، وتقارير التشريح المرضي ٦٣٩ (٧٨,٨%) ، وشهادات الوفاة ٢٠٤ (٢٥,٢%). بعد ملاءمة مجموعة من النماذج اللوغارتمية — الخطية لمصادر البيانات الثلاثة وجدنا أن المصادر الثلاثة مترابطة إحصائياً. تشير طريقة الالتقاط وإعادة الالتقاط إلى إغفال ٣٨٤ حالة، بافتراض أن عدد الحالات التي قدّر التبليغ عنها هو ١١٩٥ حالة سرطان. وعلى ضوء ذلك، فإن نسب التحقق من السجلات الطبية قد بلغت ٥١%، و٥٣% لتقارير التشريح المرضي، و١٧% لشهادات الوفاة، و٦٨% للسجل الكلي. ولدى تقييم درجة الوثوق، وجدنا أن الاختلاف الكبير الحاصل بين البيانات المستخلصة والتي أعيد استخلاصها كان أعلى لدى فحص مرحلة الداء (٤٤%)، ثم لدى الترميز النسيجي والسلوك (٢٥,٦%). بينما كان الاختلاف ضئيلاً في تاريخ التشخيص (٣٦%) ودرجة الداء (٣٦%). وبشكل عام، كان ثمة اتفاق في أوجه، بالنسبة للجانبية (٩٥%)، تلاها ترميز الموقع الابتدائي (٩٠%)، وأسس التشخيص (٨٥%). بلغت نسبة تفاوت الاتفاق في وصف الورم (الموضع، والفحص النسيجي، والسلوك، ومرحلة الداء) ٥٧%.

الخاتمة: يحتاج سجل السرطان إلى إضفاء تحسينات جوهرية، على مستوى المستشفى، بالنسبة لإكمال عملية التبليغ ونوعية البيانات. سيساعد استخدام مصادر البيانات العديدة وتقدير الحالات المغفلة في التأكد من إكتمال تسجيل الحالة.

المدونات الطبية السعودية ٢٠٠٣،٢٣ (١-٢): ٦-٩

Erratum

In the last issue (Vol 22, Nos 5-6), the name of Dr. M. Zuheir Al-Kawi, the Arabic text editor of the Annals of Saudi Medicine, inadvertently appeared with the names of Dr. Abdulrahman Alrajhi and Dr. Abdullah Al-Arifi in the Arabic version of the two papers of the American College of Physicians (ACP). Since only Dr. Alrajhi and Dr. Al-Arifi were granted permission by the ACP for translation and republication, this correction is deemed necessary. However, the contribution of Dr. Al-Kawi as the Arabic text editor is acknowledged.

تصحيح

ظهر اسم الدكتور محمد زهير القاوي محرر النصوص العربية في المدونات الطبية السعودية مع اسم كل من الدكتور عبد الرحمن الراجحي و الدكتور عبد الله العريفي في النص العربي لمقالتي كلية الأطباء الأمريكية في العدد السابق (العدد ٥-٦ ، المجلد ٢٢ ، ٢٠٠٢ ، ص ٤٢٦-٤٥٠)، و بما أن الدكتور القاوي هو محرر النصوص العربية للمدونات الطبية السعودية و لم يكن ضمن من تم منحه حقوق النقل و الترجمة من قبل كلية الأطباء الأمريكية فإننا نصحح ذلك هنا لكل من الدكتور الراجحي و الدكتور العريفي و القراء، كما نشكر الدكتور القاوي على مساهمته التحريرية، و لذا لزم التنويه.

المحرر

Annals of Saudi Medicine - Volume 23, Numbers 1-2, pages 1-115

المدونات الطبية السعودية

رئيس التحرير: الدكتور محمد أختر

هيئة التحرير

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الدكتور عبدالعزيز المشاري
الدكتور عدنان عزت
الدكتور محمد زهير القاوي
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الدكتور سلطان السديري
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محرر الإحصاءات بشير خان

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محرر النصوص العربية: الدكتور محمد زهير القاوي
محرر فني: رينه دايمكان

مساعدوا التحرير:
صاموئيل منحاس
مونيك كارتزان
فلورانتينو كابيلي

المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي - جامعة الملك سعود، صندوق بريد ٢٩٢٥ - الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ - الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي:

مكتب المطبوعات ر. إ. (٣٦)
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الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخة بأي شكل وبأي وسيلة سواء أكانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إليكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.

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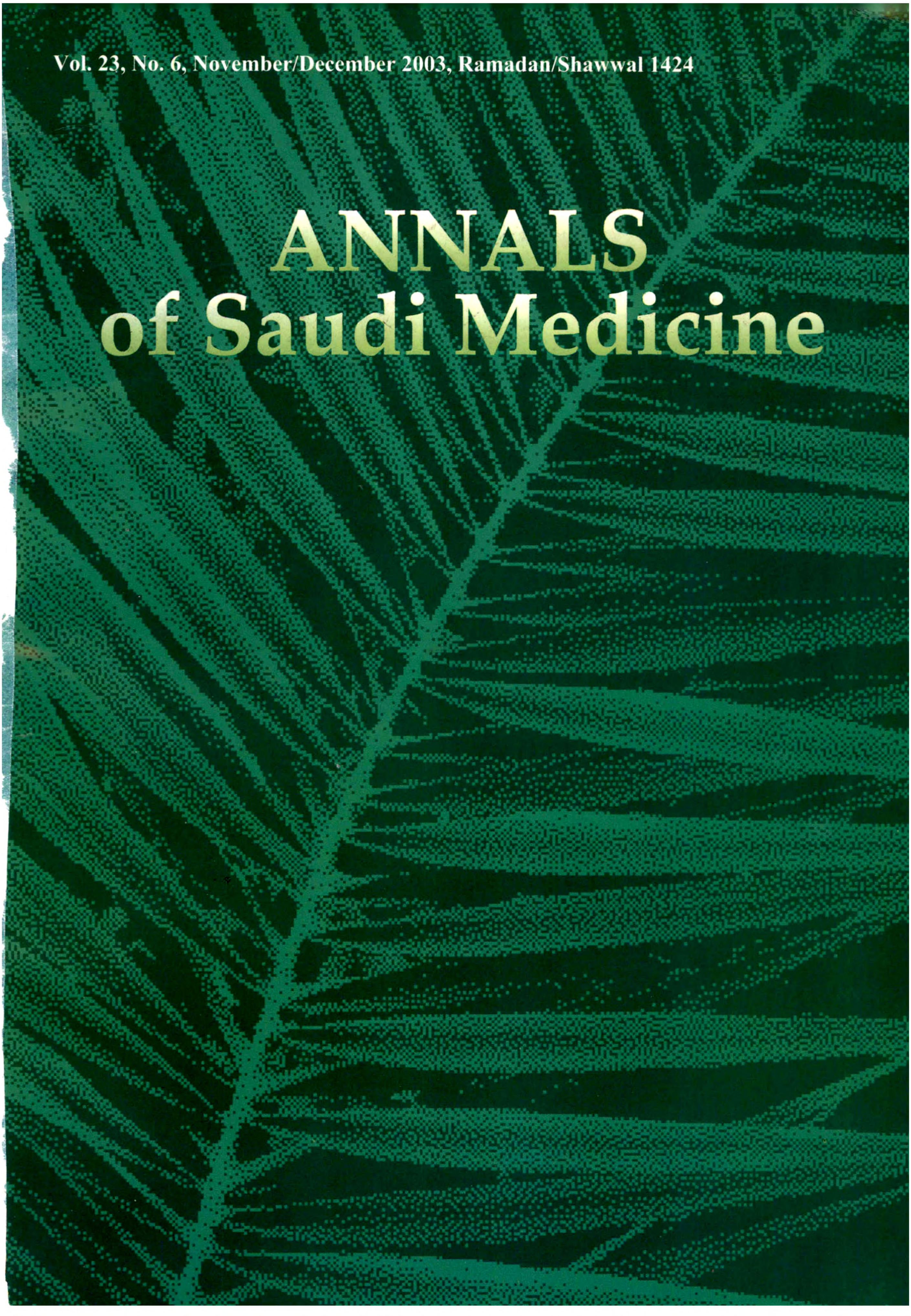

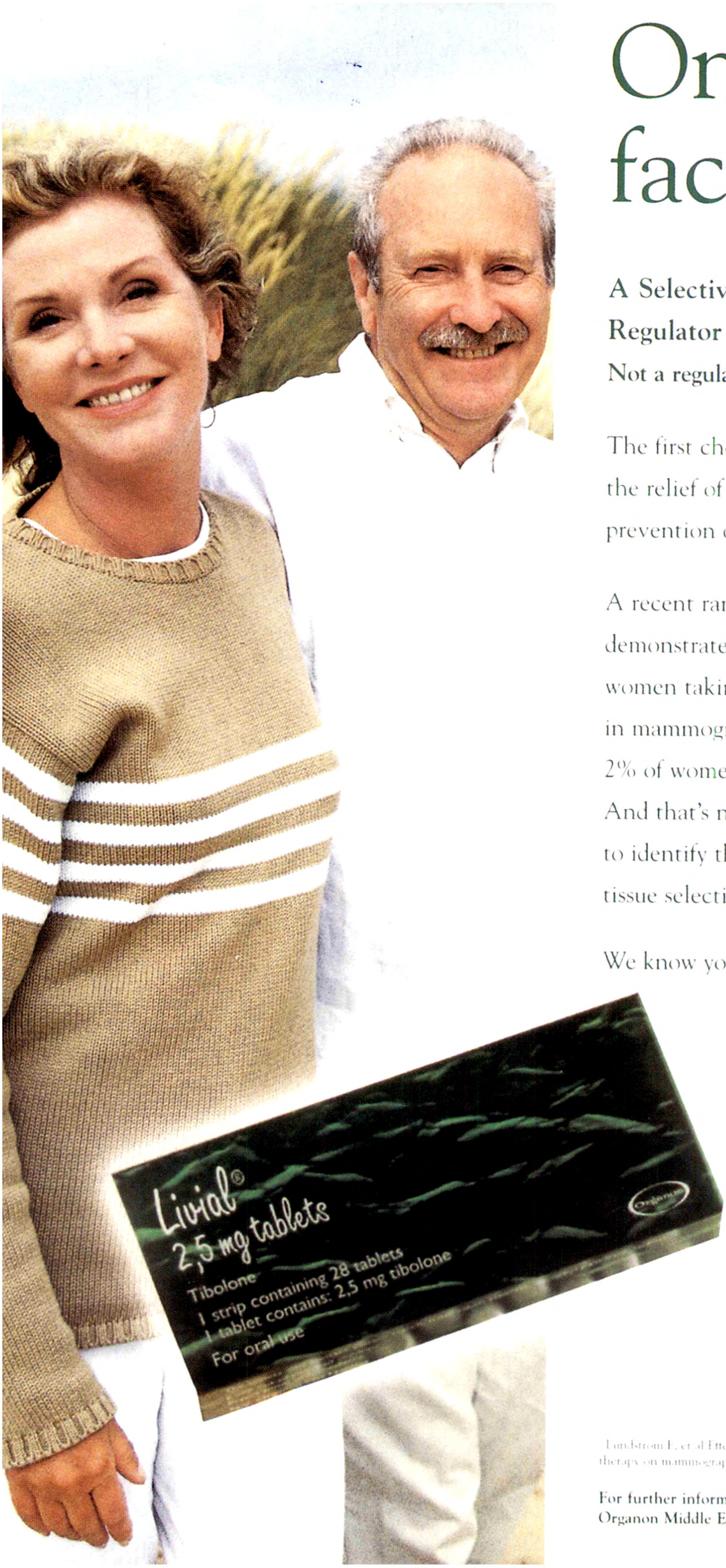
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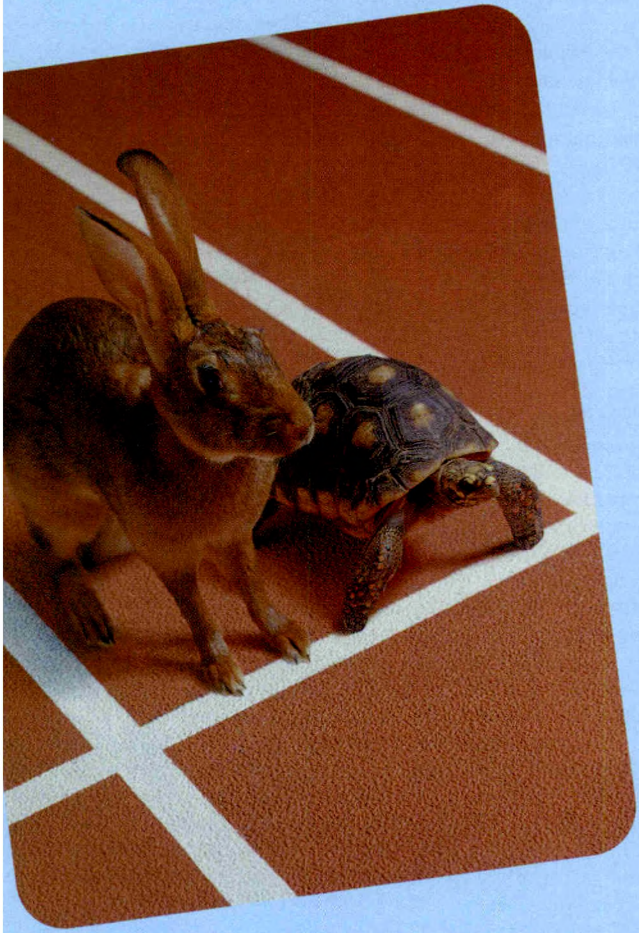

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IN2/NMAD1/9-

INHALATION DEVICES IN ASTHMA

Hanaa H. Banjar, MD, FRCPC

Hospital admissions rates for asthma have increased noticeably since the mid-1960s.[1] In New Zealand, in the 0 to 14-year age group, admissions have increased tenfold in 15 years (63 per 100 000 in 1966 to 629 per 100 000 in 1981).[1] The major role of inhalers in the management of asthma and other respiratory disorders has only developed over the past 40 years.[2] The introduction of the pressurized metered-dose inhaler (pMDI) in 1956 allowed for effective portable aerosol administration for the first time. The development of progressively more specific and effective anti-asthma therapy, and of new forms of inhalers during the 1970s and 1980s, lead to many potential improvements in quality of life for the typical patient with asthma.[2]

Inhaled β2-agonists have an important role in the management of asthma symptoms. The success of inhaled steroid therapy has greatly reduced the risk of systemic side effects from steroid treatment in patients of all ages.[2,3] In children, control of asthma can usually be achieved without the use of systemic steroid therapy, so clinically significant growth impairment is rare in well-controlled asthma.[3,4]

Conventional pMDIs have a number of disadvantages. Technical performance is not as consistent as was previously believed. Errors in use have been recognized for years as a major disadvantage. The propellants and additives in pMDIs are sometimes associated with symptoms of bronchial irritation.[5,6] Some of the disadvantages of pMDI therapy can be avoided by addition of a spacer device to the inhaler.[5] This often overcomes the coordination problems experienced by many patients with the pMDI alone, and it has beneficial effects on the quality of the aerosol inhaled by the patient, resulting in a lesser deposition of drug substance in the mouth and throat. There is variability in dose delivery, which is mainly related to electrostatic charging of the walls of the spacer. The spacer is also large, and thus less conveniently portable than pMDIs used alone.[5]

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Dry-powder inhalers offer the possibility of more predictable and less complicated therapy, and are now available for all of the major groups of anti-asthma medication.[8] The first clinically useful dry-powder inhalers were introduced in the late 1960s, and later inhalers, including the Turbohaler, [8-10] the first multi-dose dry-powder inhaler, were introduced during the 1970s and 1980s. The Turbohaler is capable of supplying as many doses as a conventional pMDI, and only a small amount of powder per dose is needed.[8-11] Comparative studies indicate that the Turbohaler might have a greater effect than a similar dose administered by pMDI (with or without a spacer).[8-11] Others [10-13] have found that the dose ratio for equal bronchodilator effect was approximately 2:1 and that the salbutamol Turbohaler (100 µg) was at least as potent as salbutamol pMDI (200 µg).[8] Agertoft and Pedersen[12] found that the budesonide Turbohaler is more effective than the budesonide Nebuhaler in the treatment of children with asthma, and concluded that the dose of budesonide should be reduced when patients are switched from Nebuhaler to Turbohaler. However, the efficacy of inhaled therapy depends on a large number of factors. These include the nature of the inhaler, drug content, propellant or carrier content (if any), mode of action, handling, the presence or absence of a spacer device, the shape and condition of the device, the size and age of the patient, the correct usage of the device by the patient, the patient's coordination, the patient's inspiratory effort, and the nature and severity of the patient's disease.

A survey of medical personnel assessed their knowledge and ability to use three widely used inhaler devices: MDI, MDI with a spacing chamber (Aerochamber), and a breath-actuated multidose dry powder inhaler.[13] Thirty respiratory therapists, 30 registered nurses, and 30 medical house staff physicians were asked to demonstrate the use of each device using placebo inhalers to answer 11 clinically relevant questions related to the use and maintenance of the tested devices. The mean (± SD) percent knowledge score (67 ± 5 percent) for respiratory therapists was significantly higher than that achieved by either nurses (39 ± 7 percent) or physicians (48 ± 7 percent) (for all $P<0.0001$). Similarly, the mean percent demonstration scores for each device were significantly higher for respiratory therapists than either the nurse or physician groups: for MDI, 97 ± 3 percent versus 82 ± 13 percent and 69 ± 24 percent, respectively ($P<0.0001$). Knowledge of and practical skills with the devices were roughly proportional to the length of time the device had been in clinical use, with Turbohaler demonstration scores being lower than either MDI or

Aerochamber scores (P=0.05 and P=0.09, respectively). More respiratory therapists (77 percent) had received formal instruction on the use of devices at school than either nurses (30 percent) or physicians (43 percent) (P<0.05). Many medical personnel responsible for monitoring and instructing patients in optimal inhaler use lack rudimentary skills with these devices.[2] Nurses and physicians seldom receive formal training in the use of inhaling devices.[3] Newer inhaling devices, designed to obviate problems of technique, are less likely to be used well by medical personnel soon after their introduction.[13]

It is of interest that these are also the most common errors identified among patients with asthma.[14] Al-Wasil et al.[15] studied the use of asthma inhalers in an adult population in Saudi Arabia in a primary health care setting and found that 93% of patients who used pMDI without a spacer and 85% with a spacer have committed at least one error in the use of these inhalers; 77% of the study population were illiterate. It is tempting to suggest but hard to prove that errors committed by patients are the result of the lack of skill in use of the devices among physicians.[14] Other investigators [15] found that patients with asthma whose physicians were more skillful with inhalers were significantly more competent themselves with inhalers than were patients whose physicians were less skillful. In a study of pharmacist dispensing of pMDIs, it was shown that specific instruction on pMDI technique during the training period and periodic continuing education during professional practice promotes better patient education.[15] We believe the same is true for pediatricians.

Most residents are never formally instructed in the use of pMDIs and spacer devices in medical school or during their residency training. They are thus dependent on self-education or passive observation to acquire the necessary skills. In addition, patient education is frequently performed by other caregivers (respiratory therapists, nurses, and pharmacists), limiting the residents' exposure to teaching and reducing their need to acquire these skills. Most authors[14-16] therefore believe that it is important to address these deficiencies during residency training. This can be done in general pediatrician clinics, in subspecialty clinics, or during the care and teaching of hospitalized patients with asthma. Despite substantial involvements in asthma management, pediatricians-in-training have significant inadequacies in knowledge of the practical and theoretic aspects of metered-dose inhaler and spacer use. The asthma specialist may need to take a leading role in the development and implementation of educational programs on inhaler therapy.

In this issue, Dr. Al-Shehri compares three inhaler devices in a pediatric population, the first such study in Saudi Arabia.[17] The findings are similar to previous studies of poor technique, as only 25% of the study population completed the assessment successfully. His findings confirm the need for proper asthma educational programs across the country for both patients and medical staff.

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ORIGINAL ARTICLE

COMPARATIVE STUDY OF DIFFERENT INHALER DEVICES IN ASTHMATIC CHILDREN

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Background: The inhaler is an important drug delivery system in the treatment of asthma, but inhaler technique is often inadequate. We assessed technique in children diagnosed with asthma, comparing the performance of three devices.

Patients and Methods: In a cross-sectional survey, 523 children (271 boys, 252 girls, ages 5 to 12 years; mean±SD 7.53±1.79 years) demonstrated inhalation technique according to Netherlands Asthma Foundation criteria during a first visit to a primary care clinic in Abha, Saudi Arabia. Patients used the device with which they were most familiar (either pMDI, Turbuhaler or Diskus).

Results: Two hundred children (38% of total population) used a pMDI, while 323 (62% of total population) used one of the dry powder inhalers‹173 (58%) the Turbuhaler and 150 (47%) the Diskus. Only 49 children (25% of the total population) completed the assessment without making a mistake. The remaining 474 (75% of the total population) performed one or more manuevers poorly. Only 80 children who used an MDI (40% of those using the device) completed 50% or more of the maneuvers correctly compared with 111 (69% of those using the device) and 100 (67% of those using the device) of those using the Turbuhaler and Diskus, respectively (P=0.001 for comparison of MDI with dry powder inhalers). Children whose mothers had intermediate school or higher education performed better than those whose mothers had less education (P=0.001). The father's education had no bearing on performance with the inhaler.

Conclusion: The inhaler technique of most asthmatic children is poor, but technique is better in children who use a dry powder compared a metered-dose inhaler. The level of the mother's education is positively associated with better inhalation technique in the child.

Key words: asthma, children, metered-dose inhaler, dry powder inhaler

Bronchial asthma is the most common chronic illness in children.[1] An increase in the prevalence and severity of bronchial asthma in both children and adults worldwide has been noted in recent years.[2] Hospital admissions are steadily increasing.[3] Children with asthma face multiple challenges that encompass learning how to cope with and manage the unique demands of this illness. These demands can involve monitoring peak airflow, administering medications, modifying the environment to limit exposure to asthma triggers, and dealing with potential side effects.

The inhaler is an important drug delivery system in the treatment of childhood asthma. Inhaler technique is inadequate in many adult asthmatics[4] and many physicians caring for asthmatic patients have poor knowledge of the proper use of inhaler devices.[5] Clear instruction with repetition is necessary when patients are about to use this type of medication for the first time. It is the responsibility of the physician to check that all patients who use inhaled medication are instructed on the correct use of their inhalers. Even if patients have been using an inhaler for a long time, regular checkups and frequent assessment of inhalation technique with follow-up education for patients with poor technique should lead to improved outcomes in patients with asthma.

Inhalers have an advantage over oral forms of asthma medicine in that, with proper technique, medication is delivered directly to the target tissue site, bypassing the need for systemic absorption and possible metabolism. Inhalation decreases the time to onset of action and reduces systemic side effects. Furthermore, inhalation reduces the amount of medication required. However, correct use of an inhaler is more difficult than swallowing syrup or a tablet. And the effect of inhaled medication depends largely on the patient's inhalation technique.[6,7] We performed this study to evaluate the technique of children with asthma and compare their performance with three different inhaler devices.

Patients and Methods

In this cross sectional survey, we recruited patients seen at Abha Medical Consultative Clinics, a primary care center located in southwestern Saudi Arabia. The

Editor's Note: Arabic abstract for this article will be published in the January-February 2004 issue.

Table 1. Distribution of patients according to sex and age.

	Turbuhaler		Diskus		MDI	
	N	Age	N	Age	N	Age
Male	69	7.24 ± 1.48	73	7.76 ± 2.08	98	7.82 ± 2.03
Female	104	6.95 ± 1.61	77	7.30 ± 1.40	102	7.45 ± 1.57
Total	173	7.13 ± 1.53	150	7.53 ± 1.78	200	7.6 ± 1.83

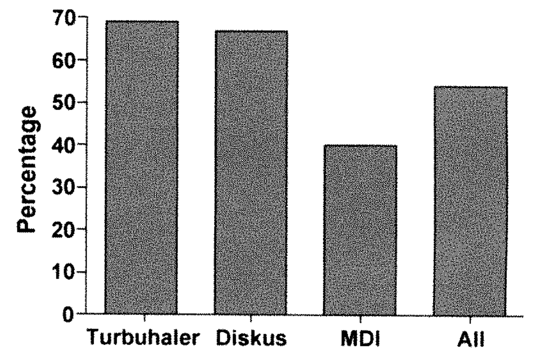
survey was done during the patient's first visit to the chest clinic. Patients were asked to demonstrate inhalation technique, using the inhaler device with which they were most familiar. A single observer using standardized checklists designed by the Netherlands Asthma Foundation scored each step. Patients had previous instruction in use of the inhaler and had been using the inhaler device for more than two months. We studied the three most commonly used types of inhalation devices: the dry powder inhalers Turbuhaler and Diskus, and a metered dose inhaler (MDI). For each patient, the inhalation technique was assessed for only one inhaler. Patients who used more than one inhaler were free to choose whichever device they found familiar and easy to use.

All data obtained were coded and entered into IBM compatible computer of the Family and Community Medicine Department, College of Medicine and Medical Sciences, King Khalid University, Abha, and analyzed using the Statistical Package for Social Science software (SPSS-Version 10). The frequency and percentage of patients who failed to perform steps of the inhalation technique were recorded, and the frequency and percentage of mistakes were calculated per inhaler. The relationship between age, gender, parent education and proper inhalation technique was analyzed by the chi-square test. The limit of statistical significance was set at *P*<0.05.

Results

Five hundred twenty-three patients referred for evaluation for asthma completed this survey. Two hundred and seventy-one (51.8%) were boys and 252 (48.2%) were girls. Ages ranged between 5 and 12 years (mean±SD, 7.53±1.79 years). Among the newly referred patients, 200 (38%) were using an MDI; 323 (62%) were using dry powder inhalers, including 173 (53%) using the Turbuhaler and 150 (47%) using the Diskus. The three groups were not significantly different in age or sex (*P*>0.05) (Table 1).

Only 25% of the children completed the assessment without making at least one mistake. Seventy-five percent performed poorly on one or more items. Only 54% completed 50% or more of the steps correctly (Figure 1). Only 40% using the MDI completed 50% or more of the steps correctly as compared with 69% and 67% of patients using the Turbuhaler and Diskus, respectively. The difference between MDI and the other two inhalers was statistically significant (c2=76.3, *P*=0.001) (Figure 1). Forty-four percent of male patients performed correctly 50% or more of the steps as compared with 47.6% of female patients. This difference was not statistically significant (*P*=0.08).



P=0.001 for difference between MDI and other inhaler devices.

Figure 1. Percentage of children performing 50% or more of steps correctly.

Among the 173 patients using the Turbuhaler, 94 (54.3%), had difficulty with the item "hold breath for ten seconds" and 82 (47.4%) had difficulty with the item "inhale forcefully and deeply" (Table 2). Sixty-five patients (37.6%) did not hold the inhaler device in the horizontal position, and 56 patients (32.4%) did not take the inhaler device out of the mouth. Lastly, 38 (22%) missed the item "prepare the inhaler device before the maneuver."

Among the 150 patients using the Diskus inhalers, 77 (51%) had difficulty in performing the item "continue slow and deep inhalation" and 75 patients (50%) could not perform the item "hold breathing for 10 seconds" (Table 2). Fifty-seven children (38%) did not hold the device in the horizontal position and 50 children (33.3%) did not know how to slide the protective cover. Forty-four patients (29%) did not take the inhaler device out of the mouth. Thirty-four patients (22.7%) did not prepare the inhaler device. Lastly, 16 patients (10.7%) missed the item "place the mouthpiece between lips and teeth."

Table 2. Steps in the correct use of Turbuhaler, Diskus, and metered-dose inhaler devices and error rates for each step.

Type	Items	Number performing incorrectly	% performing incorrectly
Turbuhaler	1. Prepare the device before maneuver.	38	22.0
	2. Keep the device horizontal.	65	37.6
	3. Place the mouthpiece between lips.	19	11.0
	4. Inhale forcefully and deeply.	82	47.4
	5. Take the device out of mouth.	56	32.4
	6. Hold breath for ten seconds.	94	54.3
Diskus	1. Prepare the device before maneuver.	34	22.7
	2. Slide the protective cover.	50	33.3
	3. Keep the device horizontal.	57	38.0
	4. Place the mouthpiece between lips.	16	10.7
	5. Inhale forcefully and deeply.	77	51.0
	6. Take the device out of mouth.	44	29.0
	7. Hold breath for ten seconds.	75	50.0
MDI	1. Shake the inhaler.	107	53.5
	2. Remove the protective cap.	35	17.5
	3. Hold the inhaler upright.	70	35.0
	4. Exhale to residual lung volume.	135	67.5
	5. Place mouthpiece between lips and teeth.	81	40.5
	6. Inhale slowly and simultaneously activate the canister and continue deep inhalation.	139	69.5
	7. Take the canister out of mouth.	81	40.5
	8. Hold breath for ten seconds	123	61.5

Among the 200 patients using an MDI (Table 2), 139 (69.5%) had difficulty with the item "inhale slowly and simultaneously activate the canister and continue deep inhalation" and 135 (67.5%) had difficulty with item "exhale to residual lung volume." One hundred twenty-three patients (61.5%) did not hold the breath for ten seconds and 107 (53.5%) did not shake the canisters before the maneuver. Eighty-one patients (40.5%) did not place the inhaler device between the lip and teeth properly and did not take the inhaler device out of the mouth. Seventy patients (35%) did not hold the canister upright. Thirty-five patients (17.5%) forgot to "remove the protective cap."

Forty-two percent of children whose mother's education reach intermediate school or more completed all the inhalation technique steps without difficulty as compared to 16.7% of children with mothers with less education (P=0.001). The difference between children whose father's education reached intermediate school or more and those with less education was not statistically significant (P=0.14).

Discussion

Successful management of asthmatic patients depends on achieving adequate delivery of inhaled drug to the lung. The first pressurized aerosol inhaler was introduced in the 1950s.[8] One of the first clinical trials was published by Freedman in 1956,[9] using a pressurized inhaler called Medihaler (Riker Laboratories). Metered-dose inhalers have become a cornerstone in the management of asthma, with production exceeding 300 million per year.[10] However, there is increasing evidence to show that a large proportion of asthmatic patients do not benefit fully from their anti-asthma drugs simply because of poor inhaler technique with MDIs.[11] This has resulted in the development of user-friendly dry powder inhalers. In spite of growing awareness that proper inhalation technique is important in patients diagnosed with asthma,[12] our results show that 75% of the patient sample could not use their inhaler as prescribed. One explanation for this may be that direct physician observation of inhaler technique may be infrequent or inaccurate. This may be because clinicians do not realize the importance of technique assessment, because of time constraints during clinic visits and because many other health professionals responsible for patient education in inhaler technique often do not understand the factors responsible for the optimal delivery of the inhaled medication.[13]

The steps included in the inhalation technique are very important in achieving the maximum benefit from the inhaler device. For example, to mix the medication with the propellant, an MDI must be shaken well before the inhalation maneuver. The mouthpiece has to be placed between the lips and teeth to prevent the medication from setting on the lips or teeth. The patient has to activate the canister while simultaneously inhaling slowly. The slow inhalation should be continued after the activation and the patient should hold his or her breath for 10 seconds. If the patient inhales too fast, impaction in the pharynx is increased. Breath holding is necessary to avoid the medication being exhaled before it can enter into the lungs. The dry powder inhalers have to be prepared before use; each inhaler has its own procedure. If such inhalers are not prepared well before usage, no medication is available for inhalation. Just as with the MDI, the mouthpiece of the dry powder inhalers has to be placed between the lips and teeth. Unlike with MDIs, patients using a dry powder inhaler should inhale strongly and deeply. Strong inhalation is necessary because the medication must have enough momentum to reach the lungs. After the inhalation, breath holding for ten seconds is also required with dry powder inhalers.

Approximately half of the patients using the Turbuhaler did not hold their breath for ten seconds, and did not inhale forcefully and deeply. One-third did not hold their Turbuhaler horizontally and did not take the inhaler out of their mouth. Half of the patients using the Diskus inhalers were not able to continue slow and deep inhalation and hold their breath for ten seconds. One-third could not hold their Diskus device in the horizontal position and did not know how to slide the protective cover. Approximately two-thirds of patients using a MDI did not exhale to residual lung volume and did not inhale slowly and deeply with simultaneous activation of the canister. Other Dutch and international studies have found these two items as common errors.[14] More than half of the patients did not hold their breath for ten seconds and half did not shake the canister before the maneuver. One-third of the patients did not place the mouthpiece between the lips and teeth and did not take the canister device out of their mouth. These findings correspond with those of other international studies.[14] Our results showed no relationship between correct performance and the child's gender, which is in agreement with other findings.[15] The educational level of the child's mother was associated with better performance of inhalation technique of asthmatic children in contrast to the father's education.

Only one-quarter of patients succeeded in performing all maneuvers correctly. About two-thirds of patients using the Turbuhaler and Diskus inhalers performed more than half the maneuver items correctly as compared to the one-third of patients using the MDI. Therefore, poor inhalation technique was observed more frequently in children using a MDI than in children using Turbuhaler and Diskus devices. This suggests that correct performance with the former inhaler is more difficult to achieve than with the other devices. These findings are in agreement with other studies[16-18] that showed that the Turbuhaler inhalation technique is easier than metered-dose inhalation technique. However, this is the first study that compared the Diskus inhaler device with other inhalers as far as we know.

It is important to mention that our study did not include other factors that may affect the performance of inhalation technique in asthmatic patients—factors like the source of education on inhalation technique and the time spent with the patient and the frequency of clinic visits. In addition, children who use a MDI with an aero-chamber or spacer were not included in this survey. We concluded that the inhalation technique of the children with asthma in this study was poor regardless of the type of inhaler device used. Turbuhaler and Diskus technique was easier to perform as compared to the MDI. Physicians should be encouraged to prescribe dry powder inhaler devices, particularly when children with asthma need prophylactic inhaler treatment. In addition, comprehensive inhalation instructions are needed to assure reliable inhalation technique, and technique must be checked repeatedly at follow-up visits. Longitudinal studies indicate that inhaler technique deteriorates over time, with most patients again developing poor technique.[19]

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ORIGINAL ARTICLE

REGIONAL EXPERIENCE WITH NEWBORN SCREENING FOR SICKLE CELL DISEASE, OTHER HEMOGLOBINOPATHIES AND G6PD DEFICIENCY

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Background: Newborn screening for sickle cell disease, other hemoglobinopathies and G6PD-deficiency is one of the most important means of decreasing mortality and morbidity in high prevalence areas. Nine years experience in newborn screening in Qatif Central Hospital are summarized.

Patients and Methods: All newborns in Qatif Central Hospital had cord blood screening for sickle cell disease, other hemoglobinopathies and G6PD deficiency using alkaline and electrophoresis, agar gel electrophoresis for sickle cell disease and fluoresecent screening technique for G6PD deficiency. Families of infants with minor hemoglobinopathies and G6PD deficiency were informed about the results in the well baby clinic.

Results: From December 1992 to December 2001, 24 012 newborn were screened. 21 858 (91.03%) were Saudi and 2154 (8.97%) were non-Saudi. In the Saudi hemoglobin electrophoresis patterns, AF (normal) was found in 49.52%, hemoglobin FS (sickle cell disease) + FS Bart's (sickle cell disease with alpha thalassemia) in 2.57%, hemoglobin AFS (sickle cell trait) + AFS Bart's (sickle cell trait with alpha thalassemia) in 21.14%, and alpha thalassemia (based on elevated Bart's hemoglobin $\geq$2%) in 35.68%. G6PD deficiency was found in 37.02% and 21.27% in males and females, respectively. Of 563 Saudi newborn with a presumptive diagnosis of sickle cell disease, 48 (8.5%) did not come to the hematology clinic or were not contactable. The diagnosis of sickle cell anemia or sickle thalassemia was confirmed in 513 patients, and 2 cases were found to have sickle cell trait on repeat testing. Many parents found it hard to accept the initial diagnosis and the resulting impact on their relationship with one another.

Conclusion: Prevention and early identification of sickle cell disease, other major hemoglobinopathies and G6PD deficiency remains the cornerstone of management of these diseases. The main barriers to successful neonatal screening for hemoglobinopathies are the level of the education and deficiency in manpower. We recommend including newborn screening for hemoglobinopathies and G6PD deficiency in the national hypothyroidism screening program in the eastern province and the establishment of a special center for hemoglobinopathies with a high standard of medical care in Qatif.

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As infant mortality declines, genetic disorders emerge as important causes of early death and chronic disabilities.[1] The hemoglobinopathies are one of the biggest genetic problems in the Arabian Peninsula.[2,3] Newborn screening for sickle cell disease and other hemoglobinopathies is one of the most important methods of decreasing mortality and morbidity. Programs of cord blood screening for hemoglobinopathies by electrophoresis at birth have been available for the past 25 years in a few centers in Saudi Arabia, but none of these centers are connected to the Ministry of Health.[4-7]

The initial report of neonatal screening for sickle cell disease, hemoglobinopathies and G6PD in our area noted that the population in Qatif is at high risk for sickle cell disease, other hemoglobinopathies and G6PD deficiency.[2] The prevalence of sickle cell diseasewas 2.4%, sickle cell trait 28.2%, alpha thalassemia 28.0%, and G6PD deficiency was 37.9% in males and 22.8% in females. Screening, which was initiated in December 1992 and funded by the Ministry of Health for one year, included hospitals and primary health care centers in Qatif and Alahasa. The project was initiated under ideal conditions, but after the first year the general consensus was that the conditions of Ministry of Health hospitals were not good enough to continue the program. Screening continued only at Qatif Central Hospital.

Increased survival in children with sickle cell disease is primarily due to improvements in pediatric medical care, especially in the management of infectious complications. The accurate identification of the major hemoglobinopathies at birth helps to prevent or allow for proper management of complications that can reduce mortality.[8-14] In addition, the identification of sickle cell trait at birth provides an opportunity to educate parents about its implications when their babies get older. The identification of the couple at risk of having a child with sickle cell disease will have a more profound effect on public health than the identification of the sickle cell infant.[15]

The primary objective of this screening program was to identify all newborns with hemoglobinopathies and G6PD deficiency and to follow babies with clinically significant hemoglobinopathies. Additionally, the program provides education, genetic counseling and family studies for all babies who have any major hemoglobinopathies. The purpose of this paper is to report our 9-year (1992-2001) experience with a regional newborn hemoglobinopathies and G6PD deficiency-screening program.

Patients and Methods

Virtually all newborn of Qatif Central Hospital since December 1992 are screened for hemoglobinopathies and G6PD deficiency. For about six months in 1996 and seven months in 1997 screening was stopped due to a shortage of chemicals.

Because Qatif Central Hospital is located on the highway, away from many villages, people find it difficult to reach the hospital due to socioeconomic reasons. The population that usually visits this hospital is primarily of Arabian Gulf origin. They have a strong preference for consanguineous marriage, and a high percentage of unemployment among the young generation. People are mobile within the eastern province but are not constant users of this hospital because most of the staff members of the hospital are of Qatif origin. When the father or mother works in the private sector, many mothers prefer to deliver in a private hospital in the eastern province. Therefore the population included in the screening program is not completely representative of Qatif community.

The birth rate was relatively constant in Qatif Central Hospital during the period of the study. The average number of deliveries was 10 daily, with a range from 8 to 13 daily.

Cord blood samples were collected in tubes containing ethylenediamine tetra-acetic acid and transferred to the Dammam regional laboratory, hematology section. The specimens were examined to determine their suitability for testing, and testing was done only if there was sufficient blood and the conditions of the specimens were good. If a clot or hemolysis was present, the test was repeated. Alkaline electrophoresis was performed on all samples. Agar gel electrophoresis (acid pH) was done on samples in which HbS was identified. A fluorescent screening technique was used to test for G6PD deficiency.[1] The patient educator attempted to call all parents of infants with sickle cell disease or other major hemoglobinopathies before the age of two months and offer follow-up in the pediatric hematology clinic for confirmation of the results and family studies.

Parent education was an essential task of the hematology clinic. All parents were taught how to use a thermometer and how to detect clinical signs that suggested serious conditions, such as increased heart rate and respiratory distress. Parents were asked to routinely palpate their infant's abdomen to look for splenomegaly, especially when the infant looked pale. They were also informed that a temperature of 38.5ºC or above might be potentially life threatening and require medical intervention to exclude a serious bacterial infection.

Results

During the 9-year period (December 1992 to December 2001), 24 012 newborns were screened. 21 858 (91.03%) were Saudi and 2154 (8.97%) were non-Saudi (Table 1). The screening result was normal in 10 824 (49.52%) of Saudi newborns. 563 (2.57%) were identified as having major hemoglobinopathies. 10442 (47.77%) had minor hemoglobinopathies (Table 2). 4621 (21.14%) had sickle cell trait with or without alpha thalassemia. 7800 (35.68%) had alpha thalassemia based on elevated hemoglobin BART's (≥2%).[16-18] G6PD deficiency was found in 6470 (29.60%) of Saudi newborns studied, 37.02% in males and 21.27% in females. In non-Saudis, the percentages of hemoglobinopathies and G6PD deficiency were small (Table 3). Eighty-six cord blood specimens were notsuitable for testing. Another peripheral blood specimen had been extracted when infants visited the well baby clinic.

563 Saudi newborns were identified as presumptively positive for sickle cell disease. They were contacted by the patient's educator and given appointments to the pediatric hematology clinic. 515 infants appeared in the clinic at early infancy. The tests were repeated and the diagnoses of sickle cell anemia or sickle cell thalassemia were confirmed in 513 patients; two patients were found to have sickle cell

Table 1. Nationality and sex of newborns screened from 1992 to 2001.

	Total	Percentage
Saudi	21 858	91.03%
Male	11 562	
Female	10 296	
Non-Saudi	2154	8.97%
Male	1161	
Female	993	
Saudi and non-Saudi	24 012	100%

Table 2. Electrophoresis patterns in screened newborns.

Pattern*	Total Saudi	(%)	Total Non-Saudi	(%)
AF	10 824	49.52	1980	91.93
AF-BART's	5821	26.63	116	5.39
AFS	2804	12.83	45	2.09
AFS-BART's	1817	8.31	6	0.28
FS	401	1.84	1	0.04
FS-BART's	162	0.74	1	0.04
OTHERS	29	0.13	5	0.23
Total	21 858	100	2154	100

*Abbreviations: AF, normal; AF-BART's, alpha thalassemia; AFS, sickle cell trait; AFS-BART's, sickle cell trait with alpha thalassemia; FS, sickle cell disease; FS-BART's, sickle cell disease with alpha thalassemia.

Table 3. Newborns with hemoglobinopathies and G6PD deficiencies.

Disease	Saudi	(%)	Non-Saudi	(%)
FS and FS-BART's	563	2.57	2	0.09
Sickle cell trait (AFS and AFS-BART's)	4621	21.14	51	2.37
Gene frequency of HbS	0.1315		0.0128	
Alpha thalassemia (AF-BART's, AFS-BART's and FS-BART's)	7800	35.68	123	5.71
G6PD deficiency total	6470	29.52	67	3.11
G6PD deficiency in males	4280	37.02	47	4.05
G6PD deficiency in females	2190	21.27	20	2.01

trait. 48(8.5%) did not come to the hematology clinic after 3 telephone calls or they were not contactable due to non-availability or wrong telephone numbers; others refused to come to the clinic because of lack of public transportation. 37 (77%) of these presented to the hospital before the age of 4 years with manifestations of sickle cell disease. The total number of patients followed regularly during the period of the study in the pediatric hematology clinic was 506. Nine patients were lost to follow up.

Screening of families of infants with sickle cell disease found that 103 other children within these families had sickle cell disease. These children were born in other hospitals and were not included in our study. They were not known to their families to have sickle cell disease before they visited the clinic.

In the first visit to the hematology clinic to clarify the diagnosis, we tried to bring both parents, but of those 515 infants who responded to the telephone call, 181 (35%) mothers came to the clinic alone or with relatives, but not with their husbands. 118 (23%) families argued and rejected the initial diagnosis of sickle cell disease in their infants.

All infants delivered in our hospital were given appointments to the well baby clinic one month after discharge from the nursery, but only about 50% of infants appeared in the well baby clinic. In the clinic, the mothers were informed as to whether their infants had any hemoglobinopathies or G6PD deficiencies. The test was not repeated in patients with sickle cell trait because the diagnosis of sickle cell trait was regarded as final. During the last 9-year period none of these were diagnosed with sickle cell disease in our hospital.

Discussion

Since the population in the Qatif area is at high risk for hemoglobinopathies and G6PD deficiency, all infants should have the opportunity to be tested in the neonatal period by means of a national screening program. That would minimize the chance of missing affected babies who are born in or outside of Qatif Central Hospital and would be more cost effective than hospital-based program.

The effectiveness of any screening program depends on the test sensitivity and the percentage of the population screened. Our experience at Qatif Central Hospital illustrates how well a screening program can work, even if conditions are less than perfect. We attributed our inability to reach the entire targeted population to the policies of different hospitals and primary care centers in this area. In primary care centers the major obstacles were the use of heal prick micro-capillary stick sampling in infants at the time of vaccination. This has the advantage of requiring only a small volume of sample, but there is the difficulty of obtaining blood from a fearful infant. In addition, the micro-capillary containers are expensive.

A comparison of the observed number of tests done annually in this study and the number of deliveries in the Qatif area (about 10 000 deliveries annually)[23] illustrates that some pregnant mothers had been either forced to or preferred to deliver in other hospitals. Since about 257 cases of sickle cell disease are born annually in the Qatif area, less than 25% of cases with sickle cell disease were detected at birth in our center during theperiod of this study. Of the majority (75%) only a small percentage of cases would be detected by the Saudi Aramco Hospital program, which is limited to employee families.

After the diagnosis we face problems in following up cases of sickle cell disease or other major hemoglobinopathies and in convincing families to come to the hematology clinic. One of the problems is that the nursery registry is by mother's names in a community that addresses the male (father) name only. Also, the great mobility of the population leads to frequent changing of telephone numbers. Even when the parents have been contacted we face the general problem of fear of medical care, i.e., the news is worse than what is being communicated, especially if this news is considered a stigmata. Resistance to scheduled appointments was noted because many patients and families appeared without an appointment or when the hematology clinic was not open, or they refused to come because they could not afford transportation.

The most difficult and controversial program is counseling. There is no clear, universally accepted method for informing the parents that both of them have sickle cell trait.[27] We share the experience of others, who have found that the parents reproductive activity is affected after we inform them that one of their children has been identified as having sickle cell disease.[24-26] It is difficult for many people to have a clear idea of the inheritance of the illnesses in the first clinic visit. The hematologist must be flexible, imaginative and successfully and accurately deliver the information to the parents so that its significance to the future of their offspring is understood.[28-29] It is important that the information be given in very simple way to avoid more anxiety.[30]

In conclusion, the future of the screening program is dismal, mainly due to lack of manpower. The level of education and deficiency in manpower are the biggest barriers to a successful newborn screening program in this region. Our recommendations are to include the hemoglobinopathies in the national newborn hypothyroidism screening program in the eastern province, and to establish a special center for sickle cell disease with a high medical standard and a regional laboratory with back-up facilities for special test procedures to diagnose other hemoglobinopathies.

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SALMONELLA AS A CAUSATIVE ORGANISM OF VARIOUS INFECTIONS IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Patients with sickle cell disease (SCD) are susceptible to a variety of bacterial infections, including infections caused by *Salmonella* species. We sought to identify the most common infections caused by *Salmonella* spp. in SCD patients at our hospital, and to determine their mortality rates and susceptibility to commonly used antimicrobial agents.

Patients and Methods: We conducted a retrospective review of all *Salmonella* infections in SCD patients admitted to Qatif Central Hospital during the last 11 years.

Results: During the 11 years of the study, 331 episodes of *Salmonella* infection occurred in 319 patients. The incidence of *Salmonella* infection in SCD patients was 11.5% compared to only 0.65% in the general hospital population. The commonest sites of *Salmonella* infection were blood (42% of isolates), followed by gastrointestinal tract (23.5%) and the skeletal system (22.5%). *Salmonella* infection was commonly seen in patients less than 15 years of age. The case fatality rate in patients with *Salmonella* sepsis was 2.2% (3/139), but there were no deaths associated with other types of *Salmonella* infections. Ampicillin and cotrimoxazole resistance occurred in 29% and 24% of the isolates, respectively, but only 0.6% were resistant to ceftriaxone and 1.8% had intermediate resistance to ciprofloxacin.

Conclusions: *Salmonella* is a common cause of sepsis and osteomyelitis in patients with SCD in our locality. Empirical antimicrobial therapy should cover the likely pathogens, including *Salmonella* species.

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Qatif Central Hospital is the major referral hospital for the Inhabitants of Qatif, an area that has the highest incidence of the sickle cell gene in Saudi Arabia.[1,2] Patients with sickle cell disease (SCD) are susceptible to a variety of bacterial infections, which are a major cause of morbidity and mortality. This increased susceptibility to infections is related to abnormalities in the defense mechanisms of these patients, including functional hyposplenism,[3] an abnormality in the alternative pathway of complement activities,[4] and defective neutrophil function.[5] Devitalisation of the gut and bone due to repetitive vaso-occlusive crises, macrophage saturation with red cell breakdown products as a result of chronic haemolysis, and underlying splenic and hepatic dysfunction, are known to predispose patients with SCD to *Salmonella* infection. This study was designed to identify the most common infections caused by *Salmonella* spp. in SCD patients at our hospital, the mortality rate associated with these infections, and antibiotic susceptibility patterns.

Patients and Methods

A retrospective review was carried out on all SCD patients who were admitted to Qatif Central Hospital between January 1990 through December 2000, with documented *Salmonella* isolation from the blood, pus, aspirate, stool, or mid-stream urine. Patients with SCD (Hb SS genotype) were identified on the basis of a positive sickling test and hemoglobin electrophoresis. The records of these patients were examined for age at onset, sex, site of *Salmonella* infection, mortality rate, and the antibiotic susceptibility of the isolates.

Blood cultures were performed on patients with suspected septicemia by aseptically drawing 10 mL of blood from adult patients and 3 mL from pediatric patients. The blood was divided into two bottles, aerobic and anaerobic. Both bottles were incubated for 5 days at 37°C and monitored on a BACTEC 9240 (Becton-Dickinson). Subcultures were made on conventional media. Stool samples were cultured on MacConkey agar, blood agar, *Salmonella*-Shigella (SS) media, and Campylobacter media, and after 24 hours enrichment in selenite F, were subcultured on SS

Media. Cultures of urine and determination of significant bacterial counts were performed by the semiquantitative method,[6] using standardized loops. Blood agar and CLED (Cysteine-Lactose- Electrolytes Deficient) agar were inoculated and incubated overnight at 37° C, and examined after 18-24 hours for significant bacteriuria. Aspirate and pus swabs were cultured on blood, chocolate and MacConkey's agar, incubated aerobically, and on blood agar anaerobically. All isolates were identified by standard microbiological techniques.[7] Gram-negative bacilli were identified using API 20 E (la Balme les Grottes 38390 Montatieu, Vercien, France). *Salmonella* isolates were confirmed by serotyping using Difco and Oxoid antisera.

Antibiotic susceptibility tests were performed on *Salmonella* isolates by the disc diffusion method using NCCLS guidelines.[8] The concentration of antibiotics in the discs used were as follows: ampicillin 10 µg, cotrimoxazole 25 µg, cefotaxime 30 µg, ceftriaxone 25 µg, chloramphenicol 30 µg, and ciprofloxacin 5 µg.

Results

During the study period, 2890 SCD patients with suspected infections were admitted to our hospital; 319 of them had 331 episodes of *Salmonella* infection for an incidence of 11.5%. Of these, 189 were males (59.2%) and 130 (40.7%) were females; 35% of infections occurred in patients less than 10 years of age, and 76% occurred in patients less than 20 years of age. The incidence of *Salmonella* infections during the same period in the general hospital population was only 0.64 %.

The 331 *Salmonella* isolates were distributed as follows: 139 from the blood, (sepsis/severe sepsis), 75 from the skeletal system (60 osteomyelitis, and 15 septic arthritis), 78 from the gastrointestinal tract, 22 from soft tissues, including two isolates from conjunctivitis, six from splenic abscesses, and 11 from urinary tract infections. The distributions of *Salmonella* spp. isolates according to patient age and site of infection are shown in Table 1.

All *Salmonella* species from blood were community-acquired infections. The most commonly affected age group was 1 to 20 years of age, with a peak in the 6 to 10 year age group, but there were no cases over the age of 40 years. Seventy-seven percent (58/75) of *Salmonella* isolates from the skeletal system were in patients less than 20 years of age. The tibia was the most common site followed by the humerus, while the knee followed by the hip were the most commonly affected sites in patients with septic arthritis.

Six *Salmonella* isolates were from patients with splenic abscess for an incidence rate of 0.2%. These were 5 males and one female, ranging in age from 4 to 26 years. All presented with fever, abdominal pain and a tender enlarged spleen. Four grew *Salmonella* spp. from blood cultures, while the other two grew *Salmonella* from the splenic abscess. Serotyping of *Salmonella* isolates was available for 228 strains of the 331 isolates. Ten isolates were *Salmonella typhi,* all from patients with sepsis. No patient had osteomyelitis caused by *Salmonella typhi.* The rest of the strains were distributed in the enteritidis serovars, as shown in Table 2. There was no significant difference in the serotypes between patients with osteomyelitis or sepsis.

Twenty-nine percent of our isolates were resistant to ampicillin, 24% were resistant to cotrimoxazole, 5% were resistant to amoxicillin-clavulanate, 14% were resistant to chloramphenicol, 2 isolates (0.6%) were resistant to ceftriaxone, and one produced extended-spectrum ß-lactamase (ESBL). No strains resistant to ciprofloxacin by the disc diffusion method were

Table 1. Distribution of *Salmonella* spp. according to age and site of isolation.

Site of isolation	No.of isolates	Patient age (years)								Frequency of isolation
		<1	1-5	6-10	11-15	16-20	21-25	26-30	>30	
Blood	139	2	10	37	32	28	12	14	4	42%
Osteomyelitis	60	-	6	11	19	10	9	3	2	18%
Septic arthritis	15	-	1	3	6	2	1	1	1	4.5%
GIT	78	-	14	19	24	3	6	7	5	23.5%
Soft tissues + Splenic abscess	28	-	5	8	6	3	3	1	2	8.4%
Urinary tract	11	-	-	1	1	2	4	2	1	3.3%
Total	331	2	36	79	88	48	35	28	15	

GIT=gastrointestinal tract

Table 2. *Salmonella* serovar distribution in sickle cell disease patients.

Serovar/Group Infection site	*S. typhi*	*Salmonella* Group B	*Salmonella* Group D (non typhi)	*Salmonella* Group C1	*Salmonella* Group C2	*Salmonella* ser. Paratyphi A	*Salmonella* ser. Cholerasuis	Total
Blood	7	34	29	12	8	10	-	100
Skeletal system	-	22	15	6	-	-	1	44
GIT	3	29	12	4	-	-	-	58
Soft tissue	-	10	4	-	2	-	-	16
Urine	-	6	2	2	-	-	-	10

GIT=gastrointestinal tract

detected, but 6 isolates (1.8%) had reduced ciprofloxacin susceptibility; 32.4% of *Salmonella* strains were resistant to two or more antibiotics.

Three of our SCD patients admitted with severe sepsis died in the ICU for a case fatality rate of 2.2%, but there were no deaths in other types of *Salmonella* infections.

Discussion

Patients with SCD are known to have an increased susceptibility to severe bacterial infections compared with the population at large.[9,10] Physicians have long recognized that patients with SCD have a propensity for developing *Salmonella* infections. The reason for the increased susceptibility of patients with SCD to *Salmonella* infections is not known, but several factors have been incriminated, including hyposplenism, and a defective complement system that hinders phagocytosis of *Salmonella*.[11,12] To this can be added impaired macrophage function resulting from phagocytosis of red blood cell breakdown products, which reduces the capacity of these cells to ingest and kill *Salmonella*.[13]

In our study, *Salmonella* species were the commonest organism isolated from blood cultures. *Salmonella* species were encountered in 40.8% of all episodes of sepsis in SCD patients followed by *Staphylococcus aureus* in 14.7% of the cases. The majority of *Salmonella* infections (76%) were seen in patients less than 20 years of age, and no cases of *Salmonella* septicemia were detected in the neonatal period or in those older than 40 years of age. Neonatal screening for abnormal hemoglobin, however, is not routinely done in our hospital, which can explain the low incidence of *Salmonella* septicemia in neonates. The low incidence in those over than 40 years is most likely due to the limited number of patients with SCD who survived after the age of 40 years during the last century. It is also possible that repeated exposure to *Salmonella* antigens with the development of an increasing number of specific antibodies results in bypassing of the alternate complement pathway. Comparing the incidence of microorganisms causing sepsis in SCD patients with those isolated from the total hospital population showed that *Salmonella* sepsis was 18 times more common in SCD patients ($P<0.01$). The most common organisms causing sepsis in the total hospital population during the same period of the study were gram negative bacteria such as *E. coli*, and *Klebsiella* species.[14] This study confirms previous reports indicating an increased predisposition to *Salmonella* sepsis in patients with SCD.[9,15]

The extraordinary susceptibility of patients with SCD to *Salmonella* osteomyelitis was first described fully in 1951 by Hodges and Holt[15] and has since been confirmed in several studies.[17,18] Over 70% of osteomyelitis seen in our patients with SCD was caused by non-typhoid *Salmonella* spp. The relative incidence is four times that of *Staphylococcus aureus*. However *S. aureus* was the second most common cause of osteomyelitis, accounting for 18% of cases (a ratio of 3.9:1.) Our study confirms two previous reports from the Eastern province of Saudi Arabia,[19,20] including one from our hospital. On the other hand, *Staphylococcus aureus* was found to be the most common causative organism in SCD patients with osteomyelitis and septic arthritis in two other reports from this province.[21,22] The reason for this difference is not known. One likely explanation is that these two studies were from one centre and included a large number of patients with sickle cell trait. In our study, patients with sickle cell trait (Hb AS) did not have a greater risk of *Salmonella* osteomyelitis than normal individuals. *Staphylococcus aureus* rather than *Salmonella* was the commonest organism causing osteomyelitis and septic arthritis in patients with sickle cell trait. Our findings also confirm earlier reports[23,24] that osteomyelitis is particularly common in early age and becomes less so with advancing age.

The susceptibility of SCD patients to *Salmonella* osteomyelitis has not been fully explained, but certain factors deserve emphasis. It has been proposed that repeated intravascular sickling and vaso-occlusive episodes devitalize the gut wall, leading to frequent seeding of *Salmonella* organisms from the bowel into the blood stream.[18] The presence of repeated marrow thrombosis, infarction and necrosis would make the bone a favored site of localization, leading to osteomyelitis and septic arthritis. The frequency with which *Salmonella* sepsis has been complicated by osteomyelitis is variable in different series. In our study, 23 patients (16.5%) initially seen with sepsis subsequently manifested osteomyelitis. Our findings stress the need for effective antibiotic coverage against both *Salmonella* and *Staphylococcus aureus* when osteomyelitis or septic arthritis are suspected in SCD patients. Antibiotics could include cefotaxime or ceftriaxone combined with cloxacillin or clindamycin initially, with more specific therapy when microbiological results become available.

Splenic abscess in association with SCD was first described by Beet in 1949.[24] The increased susceptibility to infection in the presence of splenic infarcts, which are not uncommon in patients with SCD, predisposes them to the development of splenic abscess.[25] *Salmonella* spp. were the most common organisms isolated from patients with splenic abscess in our series; 66.6% (4/6) grew *Salmonella* from blood cultures collected during the febrile episodes and 33% (2/6) grew *Salmonella* from pus specimens.

Urinary tract infection, which can precipitate vaso-occlusive crises or lead to septicemia,[26] is an important cause of morbidity among patients with SCD.[27] Comparing the incidence of microorganisms causing bacteriuria in SCD patients with organisms isolated from the total hospital population indicated that *Salmonella bacteriuria* was more common in SCD patients, with a prevalence rate of 0.3% (11/2890) compared to 0.01% in general hospital population (a ratio of 30:1).

In the group with sepsis only, 2.2% (3/139) of patients in our study died. The mortality rate in our series was low compared to a 23% mortality rate reported from Jamaica.[15] The reason for the low mortality rate in our series is not known. In the Eastern province of Saudi Arabia, SCD runs a relatively milder course than elsewhere. This has been attributed to the protective effect of a high level of hemoglobin F [28] and also partly to the co-existence of the thalassaemia gene, which is present in high frequency in this area.[28] Other factors probably contribute to the low mortality rate, including a greater index of suspicion of *Salmonella* infection and earlier use of specific anti-*Salmonella* therapy in febrile episodes in SCD patients pending culture results.

We conclude that *Salmonella* is a common cause of sepsis, splenic abscess, osteomyelitis and septic arthritis in SCD patients in our locality. Physicians caring for these patients should have a high index of suspicion for invasive *Salmonella* infection, especially in patients who have had previous episodes of sepsis. Blood cultures must always be obtained and pending culture results, empirical antimicrobial therapy should be broad enough to cover the likely organisms, including *Salmonella* species.

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DISTRIBUTION AND DIFFERENTIAL DIAGNOSIS OF *ENTAMOEBA HISTOLYTICA* FROM *ENTAMOEBA DISPAR* BY THE PCR-RFLP METHOD IN CENTRAL IRAN

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Background: *Entamoeba histolytica* and *Entamoeba dispar* are two morphologically indistinguishable human protozoan parasites that are genetically distinct species. The potential invasive pathogenic *Entamoeba histolytica* and non-invasive parasite *Entamoeba dispar* can be differentiated by molecular and other methods. We used polymerase chain reaction (PCR) to determine the ratio of the two species in a population in Tehran and Karaj in central Iran.
Materials and Methods: Human stool samples (n=12 148) were randomly collected in Tehran and Karaj and examined for *E. histolytica/E. dispar* cysts with direct and formalin-ether methods. Eighty-seven (0.7%) cases were positive, of which 49 (62.8%) isolates were successfully cultured in Robinson's medium. A pair of oligonucleotide primers designed from sequence data for genomic DNA coding the 30-KD surface antigen of *E. histolytica/E. dispar* was used to amplify a 374 base-pair (bp) fragment. The electrophoretic pattern of the PCR product digested with HinfI restriction enzyme was used for differentiation of the two species.
Results: The restriction fragment length polymorphism (RFLP) pattern obtained from a standard *E. histolytica* isolate had two fragments (219 bp and 155 bp), but the standard isolate of *E. dispar* showed three fragments (155, 152 and 67 bp). Differential diagnosis of 49 isolates of *E. histolytica/E. dispar* from Tehran and Karaj using PCR-RFLP revealed that 46 (93.9%) were *E. dispar* while only 2 (4.1%) were *E. histolytica*. One person (2%) had a mixed infection and showed both patterns.
Conclusion: The differential diagnosis of the potentially pathogenic parasite *E. histolytica* from the non-pathogenic *E. dispar* is of clinical and epidemiological importance. This study demonstrated that *E. dispar* is much more prevalent than *E. histolytica* among the "cyst passers" in Tehran and Karaj in Central Iran.

Key words: *Entamoeba histolytica*, *Entamoeba dispar*, PCR-RFLP, Iran

Entamoeba histolytica is a cosmopolitan human protozoan parasite responsible for amoebic colitis and extraintestinal amoebiasis. Although 90% of infected individuals are asymptomatic, WHO estimates that every year more than 40 to 50 million cases of invasive amoebiasis occur in the world, resulting in up to 100 000 deaths.[1,2] After malaria, amoebiasis is the second most fatal human protozoan parasitic diseases in the world.[1]

Many people infected with *E. histolytica* are asymptomatic and never develop clinical symptoms.[3] What was earlier known as *E. histolytica* actually comprises two genetically distinct but morphologically identical species, one potentially pathogenic and the other non-pathogenic.[4] On the basis of biochemical, immunological and genetic data, a formal re-description of *E. histolytica* was published in 1993, separating *E. histolytica* (potential pathogenic) from the harmless commensal, *E. dispar*.[5] Diagnosis and differentiation of the two species is important in therapy and also from an epidemiological point of view. Analysis of restriction fragment length polymorphism (RFLP) and direct sequencing of various genes amplified by polymerase chain reaction (PCR) has revealed 2.2% to 17% differences in the nucleotide sequences of *E. histolytica* and *E. dispar*.[6] These findings show that PCR and restriction enzyme digestion could be used as a powerful tool for distinguishing *E. histolytica* from *E. dispar*.

In Iran, there are no accurate data on *E. dispar*. This study was carried out to determine the ratio of *E. histolytica* and *E. dispar* in a population in Tehran and Karaj in central Iran.

Materials and Methods

This study was carried out from August 2000 to February 2002 in Tehran and Karaj, the two major metropolitan areas of Central Iran. Fecal samples containing cysts or trophozoites of *E. histolytica/E. dispar* were collected, and after mass cultivation, a 374

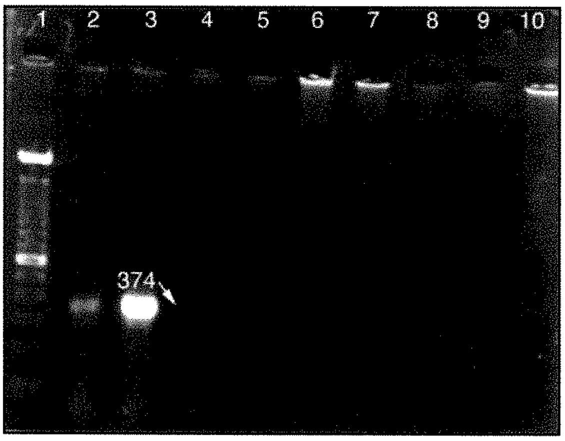

Figure 1. 1.5% agarose gel electrophoresis of the PCR product amplified by HF and HR primers. Lane 1, 100-bp DNA ladder. Lane 2, *Entamoeba dispar* (AS2IR). Lane 3, *E. histolytica* (200-NIH). Lane 4-9, *E.coli, E. hartmani, Giardia lamblia, Iodamoeba butschlii, Endolimax nana, Blastocystis hominis*, respectively. Lane 10, negative control.

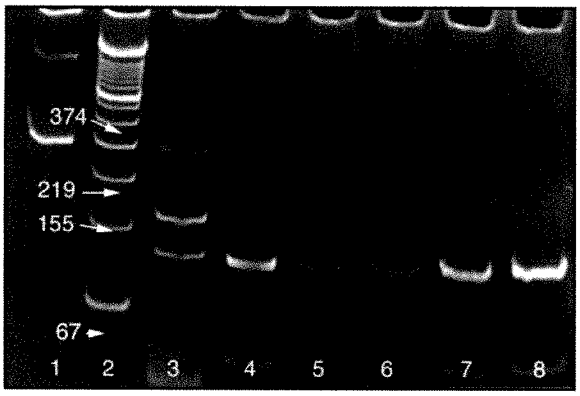

Figure 2. 10% polycrylamide gel electrophoresis of Hinfl-digested PCR products. Lane 1, undigested product (374 bp). Lane 2, 100-bp DNA ladder. Lane 3, *E. histolytica* (200-NIH). Lane 4, *E. dispar* (AS2IR). Lane 5-8, clinical samples.

base-pair (bp) sequence of genomic DNA that coded for a 30-KD surface antigen (collagen binding protein type 1) was amplified. The two species were differentiated by restriction endonuclease digestion.[7,8]

Human stool samples were randomly collected from different age groups of healthy individuals from various parts of Tehran and Karaj. Fresh stool samples were examined for ova and cysts directly and after formalin-ether concentration methods.[9] Those samples with microscopically positive results for *E. histolytica / E. dispar* cysts were inoculated into Robinson's medium for mass cultivation.[10] After three sub-culture trophozoites were harvested by centrifugation at 400 g for 5 minutes, they were washed three times with phosphate buffered saline (pH=7.2). Approximately 2x10^6 trophozoites were transferred to 1.5 mL microtube and stored at –80°C until DNA extraction.

DNA was extracted from trophozoites by phenol/chloroform and precipitated by ethanol according to the Sambrook method[11] with some modifications. Briefly, the sediment containing the trophozoite was suspended in 200 µL STE (100 mM NaCl 10 mM Tris and 1mM EDTA), 2% sodium dodecyl sulfate (SDS) and 2 µL proteinase K solution (20 mg/mL). The mixture was incubated at 60ºC for 3 hours and then boiled for 10 minutes. DNA was phenol/chloroform extracted and ethanol precipitated. The DNA was resuspended in 50 µL deionized distilled water and stored at -20ºC for PCR amplification.

One set of oligonucleotide primer HF (Hooshyar forward) (5′ AAG AAA TTG ATA TTA ATG AAT ATA) and HR (Hooshyar reverse) (5′ ATC TTC CAA TTC CAT CAT CAT) were designed and used for PCR amplification. These primers amplify a 374-bp sequence of the gene encoding a 30-KD surface antigen of *E. histolytica/E. dispar*. DNA amplification was achieved in a total volume of 30 microliters in 0.5 mL microtubes. The reaction mixture contained 10 mM Tris-HCl (pH=8.9) (final concentration), 50mM KCl, 1.5 mM MgCl$_2$, 200 nM each of deoxynucleotide triphosphate (dNTP), 20 pmol each of primers and 0.25 µL of *Taq* DNA polymerase (5U/µL) (GIBCO BRL). Then 0.5-1.0 µL of DNA was added to the reaction mixture and amplified in an automated PCR machine (Eppendorf, Hamburg, Germany, personal). Thirty cycles of denaturation at 94º C for 30 seconds (3 minutes for cycle 1), annealing at 54º C for 30 seconds and extension at 72º C for 30 seconds (5 minutes for cycle 30) were performed. Ten µL of PCR product was electrophoresed on 1.5% agarose gel (containing 1 ng/mL ethidium bromide) and visualized under ultra violet light for specific band identification. Twenty µL of PCR product was digested by Hinfl restriction endonuclease analysis (Boehringer Mannheim, Mannheim, Germany) for 2 hours at 37º C, electrophoresed on 10% polyacrylamide gel, stained by ethidium bromide and visualized under ultraviolet light.

Results

A total of 12 148 stool samples were examined. Eighty-seven (0.7%) cases were positive for *E. histolytica/E. dispar* complex cysts. All isolates were inoculated into Robinson's medium, of which 49 (62.8%) isolates were cultured successfully.

A 374-bp fragment of the genomic DNA of 49 isolates of *E. histolytica/E. dispar* was amplified using HF and HR primers. The PCR amplification products were identical to those of the positive controls [HK9 and 200-NIH strains of *E. histolytica* and AS2IR strain of *E. dispar* (zymodeme=1)]. The PCR product was seen only for *E. histolytica/E. dispar* and no bands or cross-reactivity were amplified from other intestinal protozoa, including *Entamoeba coli, Entamoeba hartmani, Giardia lamblia, Iodamoeba butschlii, Endolimax nana, Blastocystis hominis* and a negative control (without DNA) (Figure 1).

The Hinfl restriction endonuclease has been used for differentiation of *E. histolytica* from *E. dispar*.(7,8) When amplified DNA of *E. histolytica* strain HK9 or 200-NIH was digested with Hinfl, two fragments were detected (219 and 155 bp), whereas the digested PCR product of the *E. dispar* strain AS2IR showed three fragments (155, 152, 67 bp), of which 155 and 152 bp fragments were overlapped (Figure 2).

RFLP analysis of amplified genomic DNA of 49 isolates obtained from infected individuals in Tehran and Karaj showed the following findings: two persons had *E. histolytica* (4.1%) and 46 (93.9%) individuals were positive for the *E. dispar* pattern. In addition, one person (2%) was positive for both *E. histolytica* and *E. dispar* patterns (Figure 2).

Discussion

E. dispar is morphologically indistinguishable from potential pathogenic *E. histolytica*, but is not able to produce clinical symptoms. These two species could be differentiated by methods such as a specific DNA probe,[12] PCR and RFLP,[13] monoclonal antibody[2,14] and analysis of isoenzyme typing,[15] all of which are expensive and time-consuming. Comparison of methods showed that PCR could be useful as a reference test for *Entamoeba* sensitive differentiation of both species.[16] A WHO Expert Consultation on Amoebiasis stressed the need for development and improvement of simple methods for specific diagnosisof *E. histolytica* and *E. dispar* in clinical and epidemiological studies.[1] It is now clear that even in countries in which amoebiasis is endemic, such as southern Africa and India, *E. dispar* is the dominant species, and the ratio of *E. dispar* to *E. histolytica* is approximately 10:1.[3] In Cote d'Ivoire this ratio is as much as 46:1.[17] So in most cases antiparasitic therapy is not necessary.

In Iran, a number of epidemiological studies have been carried out on *E. histolytica* infection using routine stool examination techniques. However, there is no accurate data on the exact species identity of the parasites. In Iran, the prevalence rate of *E. histolytica* among healthy individuals ranges from >1% to 30%.[18] However, since it is impossible to differentiate *E. histolytica* from *E. dispar* by routine stool examination methods, we determined the ratio of *E. histolytica* to *E. dispar* by PCR. This is the first report of *E. dispar* distribution in Iran in which the two distinct species have been considered. This study showed that *E. histolytica* is rare in Tehran and Karaj and *E. dispar* (96.9%) is the predominant species in this region. This is an important finding because *E. dispar* infection does not need to be treated. It is interesting to note that in this area most cases reported as "*E. histolytica* cyst passer" are actually infected with *E. dispar*. According to the WHO expert groups it is better to identify and treat *E. histolytica* specifically,[1] but this is not possible until a simple and cheap method for detection and differentiation of the two species in endemic areas is available.

We found a low incidence of *E. histolytica* as well as mixed infection with both *E. histolytica* and *E. dispar* in Tehran and Karaj. These findings are consistent with findings in countries such as the Netherlands,[19] Canada[16] and the Philippines.[20] In an epidemiological study in Turkey all of 73 isolates of *E. histolytica/E. dispar* that were differentiated using colorimetric PCR were *E. dispar*.[21] However, *E. histolytica* has been reported in other areas such as Bangladesh[13] and Mexico as the predominant species and a large number of mixed infections have been reported.[22] Today, it is accepted that in areas where invasive amoebiasis is common, *E. dispar* is also a prevalent species.[23]

We believe that *E. dispar* is the predominant species in the central regions of Iran. A high percentage of cases reported as *E. histolytica* are actually *E. dispar*. Because previous studies on the prevalence and incidence of *E. histolytica* in Iran were not based on specific differentiation of the two species, a large-scale study of infected individuals in different areas of Iran is necessary to estimate the true incidence and prevalence of each species.

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CHANGING PATTERN OF HEPATITIS VIRAL INFECTION IN SAUDI ARABIA IN THE LAST TWO DECADES

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Background. Information on the epidemiology of viral hepatitis B, C and A in the Kingdom of Saudi Arabia (KSA) has accumulated over the last two decades. We review the changing epidemiology of these infections and suggest possible strategies for eradication.

Methods. We screened Saudi medical journals and Medline for reports dealing with hepatitis B, C and A, and analyzed official of blood donor screening data from the Ministry of Health (MOH) Central Blood Bank and the King Khalid University Hospital (KKUH) Blood Bank.

Results. Several studies from the 1980s found a high endemicity for HBV, with 5% to 10% of the population infected and prevalence varying from one region to another. In children (age 1 to 12 years), the prevalence was almost 7% in 1989, just before the addition of the HBV vaccine to the Extended Program of Immunization (EPI). By 1997, the prevalence of HBV infection in children had declined to 0.3%. Blood donor results have also shown a steady decrease in HBV infection. At KKUH, prevalence declined from 3.7% in 1987 to 1.7% in 2000. Hepatitis C infection has also shown a marked decline among Saudi blood donors at KKUH, HAV infection among children has declined from 50% in 1989 to 25% in 1997, but the infection rate is still high, reaching 50% in a few regions.

Conclusions. Hepatitis B, C, and A infection has declined in KSA in the last two decades by more than 50%. The reasons for this marked decline are multifactorial. An important reason is the adoption in the last two decades of the MOH strategy for prevention of viral hepatitis infection, which needs to continue. Improvements in the economic status of the population and the decline in illiteracy have also contributed to the decline in viral hepatitis infection.

Key words: Hepatitis B, Hepatitis C, Hepatitis A, epidemiology, Saudi Arabia

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Since the discovery of viral hepatitis B by Blumberg in the 1960s, several other hepatitis viruses have been discovered. In addition to hepatitis B virus, the most important hepatitis viruses are hepatitis A (HAV), and hepatitis C virus (HCV). Since the development of very sensitive and specific diagnostic tests, data has accumulated internationally and there is a fairly good picture of the epidemiology and transmission of these diseases. In addition, much is known about the complications and burden of illness. At least 350 million persons are carriers of HBV infection worldwide and one million die yearly due to HBV infection.[1] HCV affects at least 170 million people worldwide.[2,3] HAV used to affect a majority of the population at an early age, especially in developing countries. In the Kingdom of Saudi Arabia (KSA), information on the epidemiology of these three viruses has accumulated over the last two decades. In this article, we review the changing epidemiology of these viruses in KSA since the 1980s, including the current epidemiology, and suggest possible strategies to eradicate these infections.

Methods

To find studies on HBV, HCV and HAV infections in Kingdom of Saudi Arabia in the last two decades we screened the Saudi Medical Journal, Annals of Saudi Medicine, Saudi Gastroenterology Journal and Medline for the last two decades for any studies dealing with the epidemiology of hepatitis B, C and A viral infections in the Kingdom. We also analyzed the official data from the Ministry of Health Central Blood Bank and King Khalid University Hospital (KKUH Blood Bank) on HBV and HCV screening. Fourteen studies reported in the literature were selected for analysis.[4-16]

Results

Trends in hepatitis B virus infection

In the 1980s, several studies found a high endemicity of HBV in KSA, with 5% to 10% of the population infected.[4-6] The prevalence varied from one region to another. A community-based study of children 1 to 10 years of age showed an average prevalence of HBsAg of almost 7% in 1989, just before starting the HBV vaccination program.[7] HBV vaccine was added as the seventh primary immunogen of the Extended Program of Immunization (EPI). In 1990, another program was launched by MOH to vaccinate all children entering school. The design of the HBV vaccine program and its follow-up was part of the Preventive Strategy Program, which was designed by the Committee for Prevention of Viral Hepatitis in MOH.[8] The following strategy was adopted:

- Integrating the HBV vaccine in the EPI program.
- Vaccinating all children who entered school between 1990 and 1996, in a catch up program
- Mandatory screening of blood donors and expatriates
- Mandatory vaccination of health personnel
- Voluntary vaccination of risk groups, starting in 1990
- Health education, especially for medical personnel

In 1997, the efficacy of the hepatitis vaccination program was evaluated by means of a stratified cluster sampling technique in all 13 regions of KSA. This community-based study detected a decline of HBV infection among Saudi children up to the age of 12 years—from 7% in 1989 to 0.3% in 1997.[9] A follow-up study in 15 positive children six months later (data not reported) showed that 7 had cleared the virus and developed immunity. However, 7 of the 8 children who were still positive were found to have an HBV-infected father, mother, sisters or brothers. This indicates a major role for familial horizontal transmission of HBV in KSA.

In the 1980s, a study of MOH blood donors showed that HBV infection averaged 5% to 10%.[4,10] Another study in 1994 showed an average 4.4% infection rate (personal communication). MOH blood donor results for HBV infection in the year 2000 showed a prevalence rate of 3.2% among persons between 18 to 44 years of age and 5.9% for persons over 50 years of age, for an average of 3.25% (Figure 1) (personal communication). In 32 793 persons who donated blood at KKUH from 1987 until 2001 (Figures 2) the average prevalence rate in 1987 was 3.7%. The prevalence rate declined steadily, reaching 1.7% in 2000.

Trends in hepatitis C virus infection

Since the discovery of HCV in 1988 and introduction of diagnostic tests for this virus, data on HCV prevalence has accumulated in KSA. In 1989, while we were performing the baseline community randomized study for HBV, we used that study to

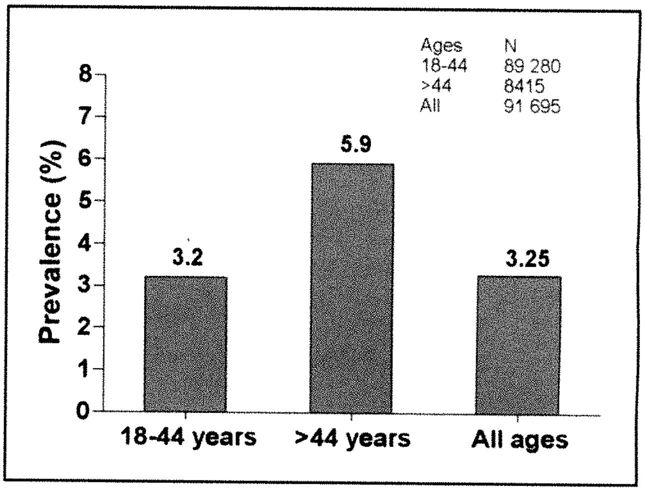

Figure 1. Prevalence of HBsAg positivity among blood donors at the Ministry of Health in the year 2000.

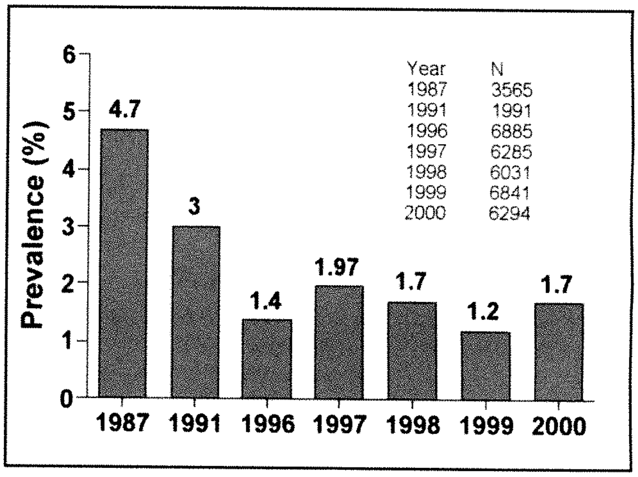

Figure 2. Prevalence of HBsAg positivity among blood donors at King Khalid University Hospital from 1987 to 2000.

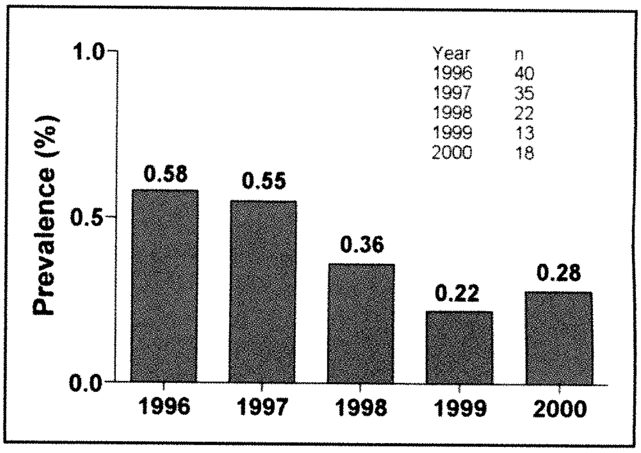

Figure 3. Age-adjusted prevalence of HBsAg among Saudi blood donors at KKUH from 1996 to 2000 (n=32 793).

Table 1. Prevalence rates (%) of HBsAg, anti-HAV, and anti-HCV among Saudi children in 1989 (n=4575) and 1997 (n=5355), according to region.

Region	HBsAg		Anti-HAV		Anti-HCV	
	1989	1997	1989	1997	1989	1997
Riyadh	8.6	0	39.0	16.0	0.8	0.1
Gassim	3.4	0.5	62.7	31.6	0	0
Hail	2.8	0	56.0	20.4	0	0
Medina	5.8	0.8	59.5	28.2	0	0
Makkah	5.7	0	55.0	20.1	0.29	0
Aseer	10.2	1.5	44.5	19.0	0.4	0
Al-Baha	7.9	0	40.6	22.1	0.7	0
Jizan	8.8	0.7	80.0	82.0	5.6	0
Najran	5.2	0	79.1	50.3	0	0
Al-Jouf	9.0	0	60.4	47.0	1.1	0
Tabouk	12.6	0.4	76.0	45.6	0	0
Dammam	3.1	0.4	38.4	18.2	0	0
Jeddah	3.7	0.3	51.0	17.5	0.88	0
Taif	7.5	0	19.0	9.0	1.5	0.3
Total	7.6	0.3	50.5	24.9	0.87	0.04

screen children from the age of 1 to 10 years for prevalence of HCV. The average prevalence was calculated to be 0.87%.[11] However, we used a first-generation EIA test, the only available test at that time. The results for Jizan in 1989 motivated us to conduct a community-based study in that region in 1991 among the adult population over the age of 10 years, using a second-generation test. The average prevalence was only 1.8%, which increased with age, reaching 3.5% in persons over 50 years.[12] When we screened 5350 children aged 1 to 12 years in 13 regions of KSA in 1997, using a third-generation EIA test and a confirmatory test using a recombinant immunoblot assay (RIBA), the prevalence was only 0.04% (Table 1). We also analyzed 32 793 Saudi blood donors from 1996 to 2001 at KKUH. The prevalence decreased steadily from 0.58% in 1996 to 0.28% in 2001 (Figure 3), which is a decline among blood donors of more than 50% over 4 years. According to Shobokshi,[10] there was a decline from 2.7% in 1993 to 1.2% in 1999 among Saudi and non-Saudi blood donors in KSA.

Trends in hepatitis A virus infection

In 1982, a study in Khaiber indicated the presence of anti-HAV in almost all individuals studied.[13] A more comprehensive, randomized community-based study in 1989 involving 4375 children from 1 to 10 years from 13 regions of Saudi Arabia showed an overall prevalence of antibody to HAV (anti-HAV) of 52%.[14] Eight years later in 1997, another comparative seroepidemiological study was conducted in the same areas, screening children from 1 to 12 years. The overall prevalence of HAV was found to be almost 25%.[15] A study by Arif et al[16] showed a reduction of anti-HAV prevalence among Saudi adults from 76% to 50.2% in 1986 and 1994, respectively.

Discussion

HBV, HCV and HAV have shown a marked decline (more than 50%) in KSA over the last two decades (Table 1). There are important causes for this decline that are common to all three viral infections.[17-20] Most important in KSA are the marked socioeconomic changes. Thanks to the Government Real Estate Bank modern houses have been built in all regions of KSA. Thus, hygiene and sanitary conditions have markedly improved. The other common factor is the decline of illiteracy in KSA, which is now about 10% compared to over 90% 40 years ago due to the comprehensive mandatory basic education system for boys and girls in KSA.

According to the World Health Organization,[1] half of the improvement in health indicators in a community can be attributed to improvements in education. However, when we look at each of these three viruses separately we find additional factors that have affected the change in their epidemiology in KSA over the last two decades. The most important factor responsible for the decline in HBV infection was the introduction of the HBV vaccination program in 1989 for all infants at birth and in 1990 for school children. Under this program, all Saudis under the age of 18 years were supposed to have been vaccinated by 2002, and all children under the age of 14 years were supposed to have been vaccinated at birth by 2002. The HBsAg carriage rate declined from 6.7% in 1989 to 0.31% in 1997 among children under the age of 12 years. Blood donor studies indicate a decline of slightly more than 50% in HBV prevalence from the 1980s to 2001. Besides improvements in hygiene and in the socioeconomic status of the population and education system, the rapid decrease of posttransfusion-related infection is due to a safer blood supply and more widely practiced infection control procedures among medical personnel.

All these factors apply to the decline in HCV prevalence except for the lack of an available vaccine against this virus. The marked difference in HCV infection between 1989 and 1997 among Saudi children under the age of 12 years is mainly due to improved diagnostic tests. Since HCV infection among children is rare, inter-family and sexual transmission is very low,[21-23] and since the blood transfusion factor has almost been excluded, one should consider other factors that could contribute to the continuing transmission of HCV among the Saudi population. Among the possible factors are non-adherence to universal infection control precautions in medical services like hemodialysis and dental clinics, sharing of needles among drug abusers, and folk medical practices like cautery and blood letting.

It is important for epidemiologists and hepatologists to remember that marked declines in HBV and HCV infection will have no immediate impact on the current disease burden of chronic hepatitis C and B and their sequelae, primarily liver cirrhosis and hepatocellular cancer. Most likely, it will be at least 20 to 40 years before we see the effect of the decline in HBV and HCV infection on morbidity and mortality among our population. The natural course of chronic hepatitis B and C in KSA will be like that in countries that have a similar prevalence of these infections.[24-28]

With HAV infection, there is a trend toward decline in most regions of the KSA. The prevalence rate in children is approaching the prevalence rate for low endemicity[29] except in a few regions like the Jizan, which still have a very high rate of infection. Because of the mobility of the Saudi population, the continuing high rates of hepatitis A infection in some regions represent a threat to other regions where an outbreak could occur among teenagers and adults with no previous exposure. For this reason, the introduction of hepatitis A vaccination for individuals older than 2 years of age needs serious discussion. Factors to be taken into consideration in this discussion include the current morbidity and mortality related to HAV infection in the different regions of KSA, the priority of hepatitis A infection among other important infectious diseases, cost-effectiveness, and logistical aspects.

Finally, based on our analysis of all the data for the three hepatitis infections, it appears that the MOH strategy for prevention of viral hepatitis in KSA has contributed to the marked decline in prevalence rates. The MOH policy needs only to be continued. The infection control policy of health centres and hospitals also needs to be closely monitored and evaluated. More health education is needed. Another important factor, outside of health services, is the need for comprehensive water and sanitation systems in all regions of KSA. At present, only 30% of regions have good water and sanitation systems (personal communication, annual report of the Ministry of Municipal and Rural Affairs 2000/2001, submitted to Majles Al-Shorah).

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ORIGINAL ARTICLE

FREQUENCY AND LEVELS OF AUTOANTIBODIES IN HEALTHY ADULT OMANIS

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Background: A previous pilot study showed a high frequency of anti-smooth muscle autoantibody in Omani blood donors and pregnant women. We conducted this larger-scale study to investigate the frequency and significance of several autoantibodies in healthy individuals from different regions of Oman.

Methods: Sera obtained from 1537 healthy Omanis (1153 males and 384 females), ranging in age from 18 to 57 years, were tested for the presence of ten different autoantibodies using indirect immunofluorescence, haemagglutination and latex agglutination techniques.

Results: Low levels of autoantibodies were detected in 33.5%, whereas a few individuals (1.8%) showed high autoantibody titres. Anti-smooth muscle autoantibodies (ASMA) were the most prevalent (11%). Anti-nuclear autoantibodies (ANA) were the second most prevalent (7.6%). Anti-thyroid microsomal autoantibodies (ATMA) and anti-thyroglobulin autoantibodies (ATA) were present in 6.5% and 4.4% of individuals, respectively. The other autoantibodies were detected much less frequently: anti-parietal cells autoantibodies (APCA) were found in 1.6%, anti-brush border antibodies (ABBA) in 1.3%, anti-reticulin autoantibodies (ARA) in 1%, anti-mitochondrial antibodies (AMA) in 0.8%, antiglomerular basement membrane antibodies (AGBMA) in 0.7% and rheumatoid factor (RF) in 0.4%.

Conclusion: The data indicate that autoantibodies are present in healthy Omani individuals, and therefore caution should be taken when interpreting laboratory results of patients suspected of having autoimmune disease.

Key words: Autoantibodies, anti-smooth muscle autoantibodies, anti-nuclear autoantibodies, anti-thyroid microsomal autoantibodies, anti-thyroglobulin autoantibodies, Oman

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The demonstration and interpretation of autoantibodies in sera from patients is a diagnostic process in autoimmune diseases. Autoantibodies can be detected in sera of healthy individuals, but the literature clearly defines their role in specific autoimmune conditions.[1-3] The definition of abnormality related to autoantibody levels is usually based on abnormal quantity. Their presence merely supports but not confirms the diagnosis of an autoimmune disease. For a clinical diagnosis, evidence of a clinical disease and / or tissue damage should be present. Thus, abnormal autoantibody levels may indicate clinical or sub-clinical autoimmune conditions.[2] The availability of data on the frequency and levels of autoantibodies within a normal population is important for diagnosis.[1-3] Many such population studies have been performed in healthy individuals in various communities.[4-9]

Oman occupies the southeastern corner of the Arabian Peninsula and has an estimated population of 2.4 million. There are eight regions with different population densities. Muscat, the capital, is the most densely populated with a population of approximately 0.5 million. A small pilot study conducted using sera obtained from a group of blood donors and pregnant women, from Muscat city only, showed a very high frequency (31.6%) of anti-smooth muscle autoantibody.10 This led us to conduct a large-scale study to determine the frequency and titres of different autoantibodies in healthy individuals from different parts of Oman.

Methods

A total of 1537 healthy, unrelated adult Omanis, from different parts of Oman, were included in the present study (1153 males and 384 females). Individuals younger than 16 years of age were excluded. No subject had a history or symptoms of autoimmune diseases and no one was taking medications for chronic diseases. Individuals who had previously been rejected from donating blood were

Table 1. The frequency of autoantibodies in a healthy Omani population.

Auto-antibody	Titres Range (median)	Males (n=1153) No. positive (%)	Males (n=1153) No. positive (%)	
ASMA	1:20-1:640 (1:80)	93 (8.1)	76 (19.8)*	169 (11)
ANA	1:20-1:640 (1:20)	86 (7.5)	31 (8.1)	117 (7.6)
ATMA	1:100-1:6400 (1:400)	70 (6.1)	30 (7.8)	100 (6.5)
ATA	1:20-1:640 (1:40)	39 (3.4)	28 (7.3)†	67 (4.4)
APCA	1:40-1:640 (1:40)	12 (1.0)	13 (3.4)	25 (1.6)
ABBA	1:40-1:80 (1:40)	14 (1.2)	6 (1.6)	20 (1.3)
ARA	1:20-1:40 (1:20)	11 (1.0)	4 (1.0)	15 (1.0)
AMA	1:40-1:160 (1:40)	12 (1.0)	0	12 (0.8)
AGBMA	1:40-1:640 (1:40)	8 (0.7)	3 (0.8)	11 (0.7)
RF	1:20-1:80 (1:20)	2 (0.2)	4 (1.0)	6 (0.4)
Total		347 (30.1)	195 (50.8)*	542 (35.3)

*$P<0.001$ vs. males; †$P<0.05$ vs. males
ASMA =anti-smooth muscle antibodies, ANA=anti-nuclear antibodies, ATMA=anti-thyroid microsomal antibodies, ATA=anti-thyroglobulin antibodies, APCA=anti-parietal cells antibodies, ABBA=anti-brush border antibodies, ARA=anti-reticulin antibodies, AMA=anti-mitochondrial antibodies, AGBMA=anti-glomerular basement membrane antibodies and RF=rheumatoid factor.

excluded. Pregnant women were also excluded from the study. Each participant was asked to complete a structured questionnaire. Ethical approval was obtained from the Sultan Qaboos University Ethics and Research Committee before starting this project in early 1999.

A volume of 10 mL of clotted blood was extracted from each individual and serum was separated and kept frozen at –20 °C. It was thawed only at the time of testing. Tests to detect the following ten autoantibodies were conducted: anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA), anti-parietal cell antibodies (APCA), anti-thyroglobulin antibodies (ATA), anti-thyroid microsomal antibodies (ATMA), anti-reticulin antibodies (ARA), anti-brush border antibodies (ABBA), anti-glomerular basement membrane antibodies (AGBMA), and rheumatoid factor (RF). Indirect Quantafluor fluorescent auto-antibody tests[11] were used for the detection and semi-quantitation of ANA, ASMA, APCA, ARA, ABBA, AGBMA and AMA, while haemagglutination assays were used for ATA and ATMA and a latex agglutination assay was used for RF.[12]

Sera were tested at a 1:20 dilution by standard immunofluorescence techniques (Quantafluor, Kallested, USA). Positive sera were titrated to determine the relative strength of the autoantibody under test. For detection of ANA positive sera and titration, HEp-2 cells were used as the substrate. Haemagglutination assays using turkey erythrocytes with bound microsomal antigens and bound thyroglobulin antigens were used to test for ATMA and ATA, respectively (Thymune-M and Thymune T, Murex, UK). Sera were first inactivated at 56 °C for 30 minutes. Positive and negative controls were included in each micro titre plate. Sera and erythrocytes were mixed then incubated at room temperature for one hour in the case of ATMA and for 30 minutes in the case of ATA tests. The end point titre was taken as the highest dilution of the sample, giving approximately 50% agglutination of the test cells. Rheumatoid factor was determined by the latex agglutination method (Humatex RF detection kit, Germany). Sera were mixed with human gamma immunoglobulin-coated latex particles. Macroscopic agglutination was seen in sera where RF was present. An equal volume of neat serum (50 mL) was mixed with the latex particles and checked for agglutination. Positive and negative controls were always included. Positive samples were titrated to determine their exact titres.

Data analysis was performed using SPSS 9.0 for Windows. The cut-off point of the significant titres for the Omani population were determined as described by El-Roeiy and Gleicher, 1988.[13]

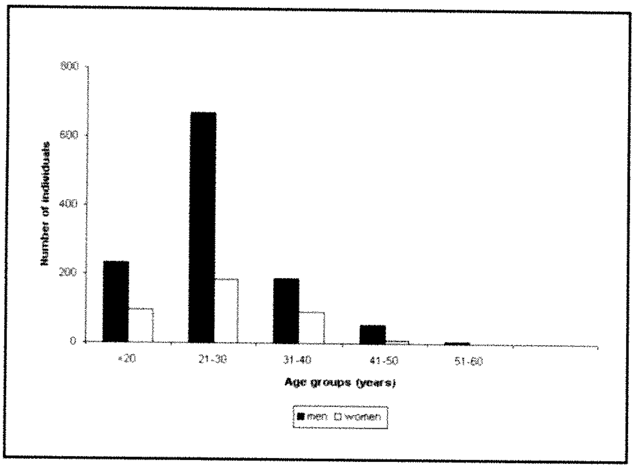

Figure 1. Age distribution of the healthy Omani study population (n=1537) (1153 males, 384 females).

Results

The majority of the individuals were young, ranging in age between 21 to 30 years, with only 7 males older than 50 years (Figure 1). Low levels of autoantibodies were detected in 33.5%, whereas a few individuals (1.8%) showed high autoantibody titres. Seventy-three individuals (4.8%) tested positive for more than one of the autoantibodies. Although some of the titres were high, there was no clinical evidence of autoimmune diseases in these persons. Autoantibodies were detected in 35.3% of the total population (Table 1). Low titre autoantibodies occurred at high frequency in both males and females (195/384 [50.8%] in females and 347/1153 [30.1%] in males; $P<0.001$).

ASMA, the most frequent autoantibody present in this population, was detected in 169/1537 (11%) of the whole cohort (Table 1). Females showed a significantly higher frequency of ASMA (76/384, 19.8%) compared to males (93/1153, 8.1%) ($P<0.001$). However, only ten individuals (0.7%) had titres greater than 1:100 for this autoantibody. When we compared the level of ASMA in different regions of Oman, the Muscat population showed the highest level (20.6%). In all other regions of Oman ASMA was detected in no more than 6%.

ANA, the second most prevalent autoantibody, was detected in 117/1537 (7.6%), with 31/384 (8.1%) in females and 86/1153 (7.5%) in males. ATMA occurred in 100/1537 (6.5%) of individuals. The frequency for ATMA was 30/384 (7.8%) in females and 70/1153 (6.1%) for males. ATMA were detected at titres ranging between 1:100 and 1:6400 (Table 1). All males positive for ATMA had lower titres than females. ATA was detected in 67/1537 (4.4%) of the whole cohort. The frequency of ATA was 28/384 (7.3%) in females and 39/1153 (3.4%) in males ($P<0.05$). Other autoantibodies generally occurred at lower frequencies, between 1.6% and 0.4%.

The cut-off values of the different autoantibodies established for the Omani population were as follows: ANA, ARA and RF ≥1:20, ATA, APCA, AGBMA, ABBA and AMA as ≥1:40, ASMA ≥1:100 and ATMA ≥1:400.

Discussion

There is considerable evidence to suggest that autoantibodies may be present in the serum of apparently healthy individuals as well as in patients with autoimmune diseases.[4-8,13-15] Many factors are known to influence the production of autoantibodies, including genetics, sex, age and viral infections.[16] In this study, healthy Omani individuals, representing most regions of Oman, showed a large number and variety of autoantibodies. ASMA were the most frequent with a prevalence of 11%. It is known that ASMA can occur at low levels in sera of healthy individuals. However, ten individuals (0.7%) had titres equal to or greater than 1:100, considered to be of clinical significance.[17] ASMA were first found in the sera of patients with chronic active hepatitis and subsequently in those with other liver diseases, viral infection, certain cancers, heroin addiction and female infertility.[18] In our study, ASMA was higher in the Muscat population (20.6%) compared to other regions of Oman where the prevalence was only 6%. The reason for these differences is not clear.

ANA are directed against a wide range of nuclear antigens and some are highly disease specific, such as in systemic lupus erythematosus (SLE) and different autoimmune disorders, thus making it of great clinical importance. However, ANA may be found in the serum of healthy individuals, as found in this study. Baig and Shere[8] found ANA to be four-fold more prevalent in females than in males in a Saudi Arabian population, whereas in our study females showed only a slightly higher frequency than males. In general, both autoantibodies and autoimmune diseases are found more frequently in females, particularly Caucasians.[3] The female preponderance of the naturally occurring ANA correlates with the increased female risk of developing autoimmune diseases in general. The total prevalence of 7.6% of ANA in this Omani group is higher than the prevalence of 4.2% found in the neighbouring Saudi Arabian population.[8]

The prevalence of ATA and ATMA were higher in females than in males in our study ($P<0.05$). Sex and age are important when evaluating the presence and titre of autoantibodies.[7,15] But as the vast majority (95%)

of our subjects were less than 40 years old, we were unable to accurately assess the frequency of autoantibodies in older subjects. This should be addressed in future studies on this population. Although two or more autoantibodies were detected in 73 (4.8%) individuals, our panel of ten is not exhaustive and the possibility of other autoantibodies in the Omani population cannot be excluded.

The results of this study show clearly the existence of autoantibodies within normal healthy individuals as has been already shown by other investigators.[4-8,15,19] This study suggests that the diagnosis of an autoimmune disorder has to be made cautiously taking into consideration that autoantibodies are present in low titres in the healthy population. The normal ranges for common autoantibodies that we have established for the Omani population may be a useful guide for diagnostic purposes. The establishment of normal cut-off values in clinically apparently healthy populations is important. Knowledge of the frequency and strength of autoantibodies in a normal population are essential benchmarks for interpreting the autoantibody results of patients from that community. Physicians seeking help from a laboratory without this data are resorting to the last refuge of the diagnostically destitute.

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ORIGINAL ARTICLE

ANTIBODIES TO GLUTAMIC ACID DECARBOXYLASE IN SYRIAN AND JORDANIAN TYPE 1 DIABETES PATIENTS AND THEIR SIBLINGS

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Background: Attempts to identify the earliest events in the autoimmune process in type 1 diabetes mellitus suggest that glutamic acid decarboxylase (GAD) is one of the first and most important autoantigens. We conducted this study to determine the prevalence of antibodies to glutamic acid decarboxylase (anti-GAD) in both Syrian and Jordanian children with Type 1 diabetes and their siblings.

Patients and Methods: Sera were obtained from 85 Syrian patients with type 1 diabetes (mean age, 13.6±5.9 years), from 45 of their siblings (mean age, 11.3±6.1 years), from 78 randomly selected Syrian control subjects (mean age, 9.9±43 years), and from 95 Jordanian patients with type 1 diabetes (mean age 13.9±65 years), from 78 of their siblings (mean age 12.3±7.1 years), and from 100 randomly selected Jordanian control subjects (mean age, 7.8±4.5 years). Sera were analyzed for anti-GAD using the enzyme linked immunosorbent assay (ELISA) technique.

Results: Prevalence of anti-GAD was 34.1% (29/85) in Syrian type 1 diabetes patients, 20% (9/45) in their siblings, 1.3% (1/78) in Syrian control subjects, 49.5% (47/95) in Jordanian type 1 diabetes patients, 23% (18/78) in their siblings, and 2% (2/100) in Jordanian control subjects. Differences between the Syrian and Jordanian type 1 diabetes groups and their siblings and controls were statistically significant. In patients with less than two years of diabetes duration, the frequency was 88.8% (16/18) for both groups. There was no correlation between sex and anti-GAD levels in either Syrian and Jordanian type 1 diabetes patients and their siblings. The positivity of anti-GAD tended to be more frequent at the age range of 5 to 8 years in siblings. Anti-GAD titers >90 ng/mL were found in 58.8% of type 1 diabetes patients and in 38% of siblings who were anti-GAD positive.

Conclusion: Syria and Jordan have prevalence rates of anti-GAD among type 1 diabetes patients and their siblings that are among the highest reported in the world. Therefore, anti-GAD may be valuable as an early predictive marker for Type 1 diabetes.

Key words: Glutamic acid decarboxylase , anti-GAD, type 1 diabetes mellitus, Syria, Jordan

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There is general agreement that type 1 diabetes mellitus (insulin-dependent diabetes mellitus, IDDM) is an autoimmune disease.[1-2] The factors that induce the selective destruction of the insulin-producing islet cells of the pancreas and sustain this autoimmune process are unknown.[3] There is increasing evidence that a close interaction exists between environmental agents and genetic susceptibility.[4]

Although autoreactive T-cells rather than autoantibodies are responsible for the destruction of ß-cells,[5] the detection and characterization of type 1 diabetes-associated autoantibodies is of great help in prediction of the disease.[6] Identification and characterization of the autoantibody-autoantigen system in IDDM is of crucial and fundamental importance in prediction and potential immunotherapy.[7]

Currently, cytoplasmic islet cell antibodies (ICAs),[8] insulin autoantibodies,[9] glutamic acid decarboxylase antibodies (anti-GAD)[10-11] and 37-k antigen antibodies are potentially useful humoral markers for such prediction.[12] However, which autoantigen is the primary target and which arises as a secondary phenomenon is still unclear.[13] The attempt to identify the earliest events in the autoimmune process suggests that GAD is one of the first and most important autoantigens.[14-15]

Patients and Methods

Sera were obtained from 180 patients with type 1 diabetes, 123 of their siblings, and from 178 from subjects not suffering from diabetes or any autoimmune disease (control group). The type 1 diabetes group consisted of 85 Syrian patients (46 males, 39 females) with a mean age of 13.6±5.9 years (mean±SD) and duration of diabetes of 3.9±2.3 years, and 95 Jordanian patients (47 males, 48 females) with a mean age of 13.9±6.5 and duration of diabetes of 4.3±2 years. The patients were recruited from the Syrian and Jordanian National Centers for Diabetes, and from other diabetes clinics in both countries. The sibling group consisted of 45 Syrian type 1 diabetes siblings (20 males, 25 females) with mean age of 11.3±6.1, and 78 Jordanian type 1 diabetes siblings (41 males, 37 females) with a mean age 12.3±7.1. The control group consisted of 78 healthy Syrian (mean age 9.9±4.3 years) and 100 healthy Jordanian (mean age of 7.8±4.5 years) subjects with no history of diabetes and/or autoimmune diseases.

Sera were analyzed for anti-GAD antibody using the enzyme-linked immunosorbent assay (ELISA) kit. With the kit, we measured the concentration of GAD-specific antibodies, and not arbitrary units. The results are given with reference to the GAD specific human monoclonal islet cell antibody clone 3 (MICA 3) and were calibrated to human IgG concentration. Samples with anti-GAD concentrations <32 ng/ml were considered antibody negative, those with values between 32-50 ng/ml were considered in the "grey area" of the test system, and samples with values >50 ng/ml were considered anti-GAD positive.

Data are presented as mean±SD. Statistical significance was determined by the correlation coefficient and chi-square test ($\chi 2$). *P* values less than 0.05 were considered statistically significant.

Results

The prevalence of anti-GAD was 34.1% in Syrian and 49.5% in Jordanian type 1 diabetes patients (*P*=0.03) (Table 1). In the siblings, the prevalence was 20.0% in Syrians and 23.0% in Jordanians (*P*=0.6). In the control groups the rate was 1.3% in Syrians and 2.0% in Jordanians (*P*=0.7). Anti-GAD prevalence rates were significantly higher in Syrian and Jordanian type 1 diabetes patients and their siblings than in their corresponding control groups (Table 1). Prevalence rates were also different between Syrian and Jordanian type 1 diabetes patients (*P*=0.03). There were no significant differences between males and females within nationalities for either the type 1 diabetes patients or their siblings (Table 1).

Although the prevalence of anti-GAD for type 1 diabetes patients with clinical diabetes of less than two years duration was 88.8% in both national groups, no significant correlation was found between the mean titer of anti-GAD and the clinical duration of diabetes. We also found no correlation between sex and the presence of anti-GAD in either Syrian or Jordanian type I diabetes patients or their siblings.

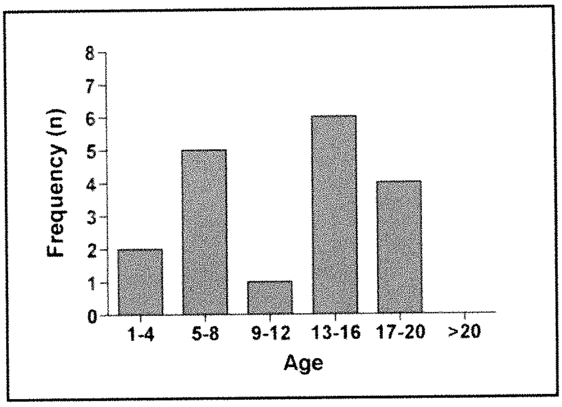

Figure 1. The frequency of anti-GAD positivity and the age of Syrian and Jordanian type 1 diabetes siblings.

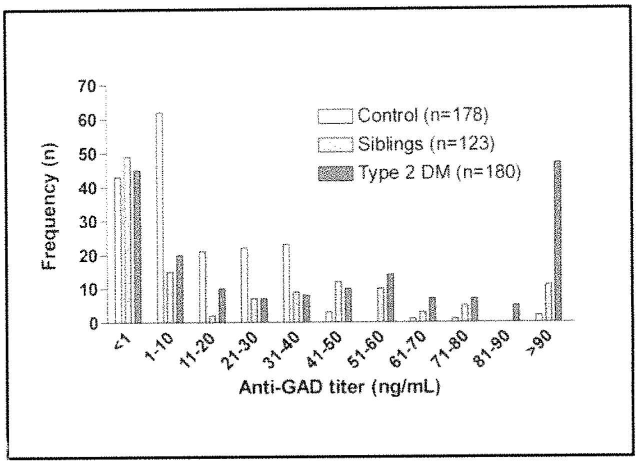

Figure 2. The frequency of anti-GAD titers in the Syrian and Jordanian populations combined.

The mean age of both Syrian and Jordanian type 1 diabetes patients who had anti-GAD was 12.9±5.3 years, and the mean age of their siblings who had anti-GAD was 10.33±4.79. In the type 1 diabetes patients the highest prevalence of anti-GAD was among the age group 13 to 16 years, while in the siblings it peaked in two age groups, 5 to 8 and 13 to 16 years (Figure 1). When subjects positive for anti-GAD were classified according to anti-GAD titer, 58.8% of the type 1 diabetes patients and 38% of the siblings had a titer over 90 ng/ml (Figure 2).

Discussion

Our data showed that anti-GAD was positive in a considerable number of type 1 diabetes patients,

Table 1. Prevalence of anti-GAD in Syrian and Jordanian populations.

	Type 1 diabetes patients	Siblings	Controls	Statistical Comparisons		
				All type 1 diabetes vs. siblings	All type 1 diabetes vs. controls	All siblings vs. controls
Syrians						
All	20.0 (9/45)	34.1 (29/85)*	1.3 (1/78)	0.0001	0.001	0.0001
Females	20.0 (5/25)	38.4 (15/39)				
Males	20.0 (4/20)	30.4 (14/46)				
Jordanians						
All	49.3 (47/95)	23 (18/78)	2.0 (2/100)	0.01	0.002	<0.002
Females	47.9 (23/48)	27.0 (10/37)				
Males	51.0 (24/47)	19.5 (8/41)				

*P=0.03 (all Syrian vs. Jordanian patients with type 1 diabetes). All differences between males and females statistically nonsignificant.

irrespective of the time since clinical onset. This finding is concordant with most other studies.[15,16] In addition, we found no correlation between sex and the positivity of anti-GAD, a finding also reported in several other studies.[17] Two reports found a female preponderance of anti-GAD, the first a report from Australia (75% females vs 63% males, P=0.03)[18] and the second from Sweden (79% females vs 63% males, P<0.001.)[19]

The highest frequency of anti-GAD in type 1 diabetes patents was in the age group 13 to 16 years, while in the IDDM siblings it was highest in the two age groups 5 to 8 and 13 to 16 years (Figure 1). No correlation, however, was found between age and anti-GAD titers. All these findings suggest that anti-GAD can be a potentially useful predictive marker for type 1 diabetes.[16-19]

To the best of our knowledge, this is the first study to determine the prevalence of anti-GAD not only in Syrian and Jordanian populations but in the rest of the Arab World and the Near East as well. Anti-GAD prevalence rates were significantly higher in Syrian and Jordanian type 1 diabetes patients and siblings than in their corresponding control groups (P<0.001, P <0.0001, P=0.002, respectively). Since the control groups were well-matched by age, sex and geographic area, our data imply that the anti-GAD would achieve a sufficiently predictive value to identify individuals at high risk of developing type 1 diabetes and to subsequently institute preventive therapy whenever such therapy becomes available. Another advantage of anti-GAD is that it is simple to perform and to standardize. By contrast, the islet cell antibody (ICA) test is difficult to standardize and is cumbersome and time-consuming. Nevertheless, several studies suggest that while the anti-GAD may have a higher specificity for type 1 diabetes prediction than the ICA test, the combination of both tests increases the sensitivity for type 1 diabetes prediction.[20-22]

While we found a similar prevalence of anti-GAD in the Syrian and Jordanian type 1 diabetes siblings, it was surprising to find a significant difference in the prevalence of anti-GAD between the Syrian and Jordanian Type 1 diabetes patient groups (P=0.03). This observation may be explained by the difference in the socioeconomic levels of the type 1 diabetes groups we studied. However, the similar results in the siblings and their related control groups in both populations do not support this explanation.

The wide geographic differences in the incidence and prevalence of Type 1 diabetes prompted us to compare our results with those of others (Table 2). The highest prevalence of anti-GAD had been among the Finnish (82%), Swedish (70%),[23] and European, and Australian (74%)(15) populations, while the lowest prevalence was among Koreans.[24] Our data showed a comparable prevalence of anti-GAD between Syrian and Japanese populations,[24] and between Jordanians and Thais.[25] Ethnic and / or environmental factors may be the cause of differences in anti-GAD prevalence observed in different populations.[23]

Additionally, insulin-dependent diabetes mellitus is associated with certain HLA Class II alleles. Most population studies have shown that HLA-DR3 and -DR4 alleles are associated with an increased risk of developing type 1 diabetes. In the last decade much evidence has accumulated suggesting that the HLA-DQ alleles, which are in linkage disequilibrium with DR, rather than the DR locus, are more closely associated with increased susceptibility for type 1 diabetes. More recent studies have shown that there is a positive association between anti-GAD and DQ alleles.[14-26,27] Thus it would be important to determine

Table 2. Prevalence of anti-GAD in different populations.

Population	Subjects	Prevalence (%)	Reference
Finnish	Type 1 DM	82	28
Swedish	Type 1 DM (new)	70	22
	Type 1 DM	15	
Australian	Type 1 DM (new)	74	15
	Type 1 DM	67	
	Siblings	6	
Thai	Type 1 DM	51	24
Japanese	Type 1 DM (new)	64	23
	Type 1 DM	82	
Chinese	Type 1 DM	39	15
Korean	Type 1 DM	30	24
Syrian	Type 1 DM	34	Present study
	Siblings	20	
Jordanian	Type 1 DM	50	Present study
	Siblings	23	

DM=Diabetes mellitus

Table 3. Levels of anti-GAD at beginning of study and after one year in 11 type 1 diabetes siblings with positive anti-GAD.

Sibling	Anti-GAD* (ng/mL)	Anti-GAD† (ng/mL)	FBS††	Insulin (U/mL)
1	74	71 ↓	70	30
2	61	63 ↑	76	1.5
3	53	106 ↑	98	29
4	65	66 ↑	85	41
5	78	73 ↓	92	8.6
6	101	72 ↓	92	3.8
7	500	819 ↑	96	4.2
8	60	95 ↑	85	4.2
9	55	58 ↑	86	22
10	54	59 ↑	66	2.3
11	50	65 ↑	245	2.8

*Initial anti-GAD level, †Anti-GAD level after one year, ††FBS=fasting blood sugar (FBS and insulin levels measured at one year.

the susceptible alleles that correlate highly with the positivity of anti-GAD among Syrian and Jordanian populations. This issue is currently being investigated.

The most important finding in our study was that Syrian and Jordanian IDDM siblings had one of the highest reported prevalence rates of anti-GAD (20% and 23% respectively). Furthermore, we found a high frequency of type 1 diabetes siblings with an anti-GAD titer of 32 to 50 ng/ml, which has been considered a grey area (Figure 2). However, while autoimmune reaction against pancreatic ß-cells may occur in many children without developing overt diabetes, in some cases type 1 diabetes may develop many years later. How many of these anti-GAD positive siblings will go on to develop diabetes is a question that can be answered only after constant and long-term follow up of these subjects. Until that issue is clarified, it seems appropriate to screen for the presence of anti-GAD in siblings of Type 1 diabetes patients.

One year after the initial screening, we re-determined anti-GAD in non-diabetic siblings who originally tested positive for anti-GAD (Table 3). We found that the levels of anti-GAD titer had increased in three subjects. The first one had normal fasting blood sugar (FBS) and plasma insulin levels. The second subject had an insulin level at the lower limit (4.2 μ/mL), and the third one had an elevated FBS (245.5 mg/dL) and a decreased plasma insulin level (2.8 μ/mL). This last sibling was diagnosed with type 1 diabetes and started on insulin therapy.

Levels of anti-GAD titer decreased in three type 1 diabetes siblings. This finding is not in agreement with those of Tuomilehto[28] and Whittingham.[20] In the Tuomilehto study the levels of anti-GAD were determined in multiple samples collected over a period of 10 years before the clinical onset of type 1 diabetes. Tuomilehto found that none of the anti-GAD positive subjects became negative during the subsequent follow up in the pediatric period.[28] In the Whittingham study (a follow-up to the Tuomilehto study), the prevalence of anti-GAD was 83% at the beginning of the study. During the 10 year pre-diabetic period the prevalence of anti-GAD was 25% in subjects who developed type 1 diabetes.[29] Moreover, the levels of anti-GAD in those same subjects did not change during the follow-up period. The discordant results between our study and that of Tuomilehto may be due to the anti-GAD assay methodology. We used ELISA technique while Tuomilehto used radioimmunoprecipitation assay technique. Differences in the groups may be another reason for this discrepancy. It is worth mentioning that there is a general agreement that anti-GAD provides the best way to predict which noninsulin dependent or type 2 patients would later need regular insulin treatment.[30] Most studies suggest that patients diagnosed with type 2 diabetes with a positive GAD index would be later reclassified as having type 1 diabetes.[31-33] The determination of anti-GAD prevalence in such Jordanian and Syrian patients will be one of our targets in the coming years.

Measurement of anti-GAD is a valuable screening tool to detect individuals at risk for developing type 1 diabetes, especially type 1 diabetes siblings. Anti-GAD testing would thus be useful for the implementation of preventive therapy for type 1 diabetes, whenever an effective and acceptable treatment becomes available.

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ORIGINAL ARTICLE

PREVALENCE AND PREDICTORS OF PREMENSTRUAL SYNDROME AMONG COLLEGE–AGED WOMEN IN SAUDI ARABIA

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Background: Research on risk factors for premenstrual syndrome (PMS) is lacking for the Gulf countries of the Middle East, a region with unique cultural features that might influence expectations and self-perception of the disease. We examined the association of PMS frequency with possible risk factors for the disease.

Methods: Using a self-report questionnaire, we surveyed all eligible young women (n=464) enrolled in the medical, nursing and medical technology/respiratory therapy educational programs at a university in Dammam. Women were asked about the frequency of symptoms during the previous six months. A stepwise multiple regression analysis was performed to determine which of several biopsychosocial and dietary factors influenced the premenstrual symptom score.

Results: At least one premenstrual symptom was experienced by 448 women (96.6%), and 176 (37.5%) had a high symptom severity score. Premenstrual symptom frequency was significantly associated with a maternal history of premenstrual syndrome, self-perception of mental stress, physical activity, consumption of sweet-tasting foods, and coffee, but these factors only explained 14% of the variability in the multiple regression model.

Conclusions: We recommend that women vulnerable to mental stress take advantage of relaxation techniques and psychotropic therapies. Moreover, women with PMS might eliminate sweet-tasting food and caffeine-containing beverages, particularly coffee, from their diet.

Key Words: Premenstrual syndrome, caffeinated beverages, cocoa-chocolate, physical exercise, mental stress, Saudi Arabia

Premenstrual syndrome (PMS) is a cyclical disorder involving behavioral, emotional and physical symptoms during the premenstrual phase. Its etiology remains controversial. Various hypothesis include biosocial and psychological causes,[1,2] endocrinological dysfunctions,[3] altered endorphin modulation of gonadotropic secretion,[4] exercise habits,[5-6] smoking, use of alcohol,[1,7] altered transcapillary fluid balance,[8] oral contraceptive use, and a diet high in beef, refined sugar products or caffeine containing beverages.[9-13] Despite considerable research, the causes of PMS remain enigmatic and further study is needed to establish stronger evidence for putative risk factors.

Most research on PMS has been done in the West or Far East. To the authors' knowledge, none has been reported from the Gulf countries of the Middle East. Cultural variations influence expectations and self-perception of disease phenomena as well as lifestyle. Cultural features in this part of the world include close-knit families in whom perceptions of health and disease have a sociological bearing. Though alcohol is not consumed for religious reasons and smoking is uncommon among women, diets rich in calories are popular, and a variety of caffeinated beverages ranging form coffee to cola drink are commonly consumed. Could these factors and others influence the occurrence of PMS? With this question in mind, the current study was undertaken to examine the association of PMS frequency with perceived stress in the daily routine of life, maternal history of PMS, a family history of depression or other mental illness, exercise habits, and consumption of beef, fiber-rich food, or sweet-tasting food items such as chocolates and deserts, intake of water and caffeine-containing beverages.

Methods

The study subjects were women enrolled at a university in Damman (Saudi Arabia) who were pursuing nursing, medical laboratory technology and respiratory therapy educational programs. Out of a total of 488 women enrolled, 9 (1.8%) students had withdrawn from all courses for that year, 4 (0.8%) were not available during the study period, and 3 (0.6%) did not wish to participate. Women taking any hormonal medication or suffering from a major gynecological problem (1.6%) were also excluded from the study. The remaining 464 eligible students participated in the study, which was conducted during a one-week period in April 1999.

Data collection was done through a self-administered questionnaire. Students were provided with explanations to questions by a group of trained researchers. The questionnaire solicited information on personal characteristics of students such as age, marital status, program of study and grade level. Information was obtained for level of physical activity (none, daily housework for at least two hours, thrice weekly sessions of walking or aerobic/rhythmic exercises for at least 20 minutes or participation in sports). Inquiry was made for perceived mental stress in the daily routine of life (none, mild, moderate and severe), a maternal history of PMS and a family history of depression or other mental illness. The dietary history included intake of sweet-tasting food items such as chocolates, cakes, sweets, deserts (<1/week, 1-3 times/week, 4-7 times/week, twice/day, ≥ three times/day) beef (<1 times per week, 1-2 times per week, ≥ 3 times per week) and fiber-rich foods such as fruits, vegetables and whole wheat products (0-1/week, 2-4 times/week ≥5/week). Intake of water or caffeinated beverages was recorded as the number of cups (1 cup=6 oz) consumed per week. Participants indicated the type of caffeinated beverage consumed from a list that included cola drinks, tea, cocoa-chocolates and coffee, including the Arab coffee "Gahwa." For frequent and regular consumers of caffeine-containing drugs, the estimates of the number of cups of a caffeine-containing beverage consumed per week were proportionately increased based on the caffeine content of the drug.

The women were asked whether they had experienced premenstrual symptoms during the last six months on three or more occasions. The questionnaire included an explicit explanation of the timing of the symptoms (one week prior to the onset of the menstrual period and generally ending a couple of days before periods or at the commencement of periods). A list of 13 symptoms plus the "other" symptom category was provided and respondents were asked to assess the severity for each symptom. A score of 1 was assigned to each symptom rated mild (daily activities not affected and no medication taken), a score of 2 was assigned to each symptom rated moderate (daily activities not affected but medication was taken) and a score of 3 was assigned to each symptom rated severe (daily activities were affected despite medication). The total premenstrual symptom score was calculated for each woman. The range of possible scores was 0 (no symptoms) to 42 (maximum of 14 severe symptoms). The total score was arbitrarily categorized by three levels: 0, 1- 9, ≥ 10. Scoring was done for each of the qualitative independent variables such as marital status, physical activity, perceived mental stress, family history of depression/mental illness, maternal history of PMS, intake of beef, fiber-rich foods and sweet-tasting foods. The quantitative independent variables included age, water intake, and caffeinated beverages per week.

Data Analysis

The total premenstrual symptom score was the dependant variable. Initially, the distribution of independent variables by premenstrual symptom score was determined and a univariate analysis of data was done. A stepwise multiple regression analysis was then done to determine which of the independent variables exerted a significant influence on the premenstrual symptom score while others were held constant. A *P* value of less the 0.05 was considered significant. Data were analyzed using SPSS.

Results

The age of the women ranged from 17 to 27 years with a mean (±SD) of 20.3±1.8 years. A majority were Saudi (95%) and not married (93.5%). More than half of the women (55.5%) were enrolled in the medical program, 25.6% in the nursing and 19.1% in the medical technology/respiratory therapy programs. Of the 464 eligible women, 448 (96.6%) experienced at least one premenstrual symptom during the last six months. The premenstrual symptom scores ranged from 0 to 33. Of the 464 women, 16 (3.4%) had a premenstrual score of 0 (no symptoms), 272 (58.6%) had a premenstrual symptom score of 1 to 9 and 176 (37.9%) had a premenstrual symptom score from 10 to 33. A large proportion of women having a premenstrual symptom score from 1 to 9 reported all their symptoms as mild (64%) whereas few women in this group reported all their symptoms as severe (5.1%). On the other hand, for women with premenstrual symptom scores from 10 to 33, only 2.2% had mild symptoms and 82.6% had severe symptoms.

A univariate analysis of the data between the premenstrual symptom score and the independent demographic variables of age, marital status, and study program or grade level showed no significant association. However, a maternal history of PMS exerted a significant influence on the occurrence of premenstrual symptoms in daughters. More women

Table 1. Distribution of women according to premenstrual (PM) symptom scores and maternal history of premenstrual syndrome, self-reported mental stress, physical activity, and intake of certain foods and caffeinated drinks.

PM symptom score	Maternal history (PMS)*		Mental stress*		Physical activity		Sweet-tasting food items*		Beef*			Fiber-rich** food*			Coffee* (cups/week)			Cocoa-chocolate** (cups/week)	
	No	Yes	Mild	Mod/sev	No	Yes	0-2/day	3/day	<1/wk	1-2/wk	>3/wk	0-1/wk	2-4/wk	≥5/wk	0	1-6	≥7	0-3	≥4
0-9	187	101	204	84	161	127	278	10	175	91	22	4	152	132	158	97	33	283	3
n=288	**67.0**	**54.6**	**67.5**	**51.9**	**69.4**	**54.7**	**62.9**	**38.5**	**62.9**	**59.5**	**66.7**	**57.1**	**67.6**	**56.9**	**54.9**	**33.7**	**11.5**	**62.7**	**38.55**
10-33	92	84	98	78	71	105	160	16	103	62	11	3	73	100	82	53	41	168	8
n=176	**33**	**45.4**	**32.5**	**48.1**	**30.6**	**45.3**	**36.5**	**61.5**	**36.5**	**40.5**	**33.3**	**42.9**	**32.4**	**43.1**	**46.6**	**30.1**	**23.3**	**37.3**	**61.1**
Total	279	185	302	162	232	232	438	26	278	153	33	7	225	232	240	150	74	451	13
n=464	**60.1**	**39.9**	**65.1**	**34.9**	**50**	**50**	**94.4**	**5.6**	**59**	**32.9**	**7.1**	**1.5**	**48.5**	**50**	**51.7**	**32.3**	**15.9**	**97.2**	**2.8**

Percentages in bold

(45.4%) whose mothers suffered from PMS had high premenstrual symptom scores (10-33) than women (33%) whose mothers did not suffer from PMS (*P*<0.01) Among women with low scores (0-9), more had a negative than positive maternal history (Table 1, Figure 1). Self-perception of mental stress in the daily routine of life was also closely associated with premenstrual symptom frequency (Figure 2). Among students with high premenstrual symptom scores (10-33), more reported moderate to severe mental stress (48.1%) than no or mild stress (32.5%) (*P*<0.01) Family history of depression or mental illness showed that high premenstrual symptom severity was more common in women with a positive history (46.9%) than those who did not have such a history (36.8%), but the results did not reach the significant level (*P*>0.05) (data not shown). An unexpected trend was observed for the influence of physical activity and premenstrual symptom frequency. A larger proportion of women who were physically active (45.3%) had high premenstrual symptom scores (10-33) compared to those women (30.6%) who were sedentary (*P*<0.01) (Table 1, Figure 3).

A significant relationship was observed between premenstrual symptom severity and consumption of sweet-tasting food items such as chocolates, cakes, and deserts (Table 1, Figure 4). Women who ate these food items frequently (≥3 times/day) had higher premenstrual symptom scores (61.5%) than those (36.5%) who consumed them less often (*P*<0.05). No significant correlation was observed between premenstrual score and intake of beef or fiber-rich food (Table 1, Figures 5 and 6). Consumption of water also did not influence the frequency of premenstrual symptoms. Relationships between different types of caffeinated beverages and the premenstrual symptom score were variable. Intake of caffeinated coffee had a significant influence on the occurrence of premenstrual symptom severity with more women having a high than a low score among those who drank ≥7 cups of coffee per week compared with those who drank less (Table 1, Figure 7) (*P*<0.05). A similar observation was made for women who drank ≥4 cups of cocoa-chocolate drinks per week but the results were insignificant in the univariate analysis (*P*=0.07) (Figure 8). Caffeinated cola drinks, tea and 'Gahwa' (Arabian coffee) showed no significant influence on the premenstrual symptom score in our study.

In model 1 of the multiple regression analysis, the total weekly intake in cups of caffeinated beverages consumed by each woman was one of the independent variables. Its relationship with the premenstrual symptom score was studied along with the other independent variables. In model 2, each caffeinated drink was analyzed as a separate independent variable and along with the other variables. In model 1, self-reported mental stress, a history of maternal PMS, physical activity, intake of sweet-tasting food items and total caffeinated beverages explained 14% of the variation in the premenstrual symptom score. Each variable exerted a significant, positive, and independent influence on symptom severity when other variables were held constant. Being married, a family history of psychiatric illness and intake of water were not significantly related to premenstrual symptom frequency in this study. In model 2 of the analysis, a similar observation was made for the association between premenstrual symptom severity and the independent variables (other than the total caffeinated beverages) as in Model 1. Among the caffeinated beverages, consumption of coffee and cocoa-chocolate drinks was found to be significantly associated with premenstrual symptom frequency (*P*<0.05). While intake of 'Gahwa" (Arabian coffee) showed a positive association with premenstrual symptom score at the 1% level, the influence of other caffeinated drinks such tea and cola was insignificant (*P*>0.05).

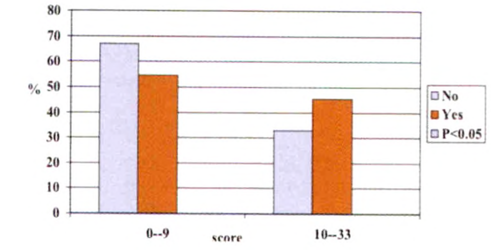

Figure 1. Distribution of women by premenstrual symptom score and maternal history of premenstrual syndrome.

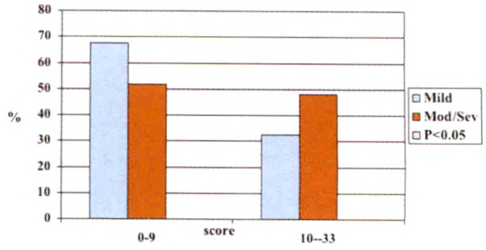

Figure 2. Distribution of women by premenstrual symptom score and self-reported mental stress.

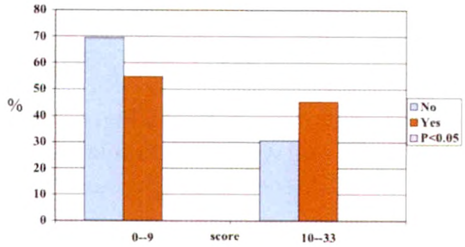

Figure 3. Distribution of women by premenstrual symptom score and physical activity.

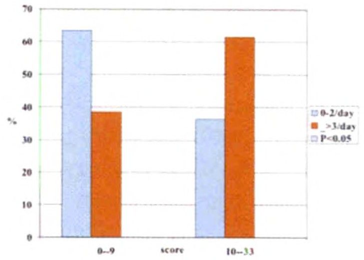

Figure 4. Distribution of women by premenstrual symptom score and intake of sweet-tasting food items.

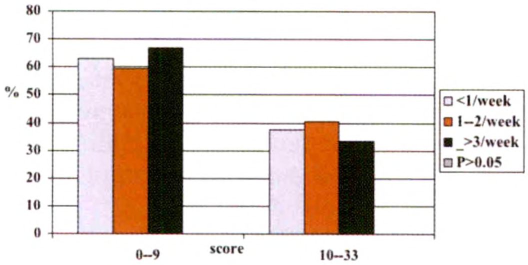

Figure 5. Distribution of women by premenstrual symptom score and intake of beef.

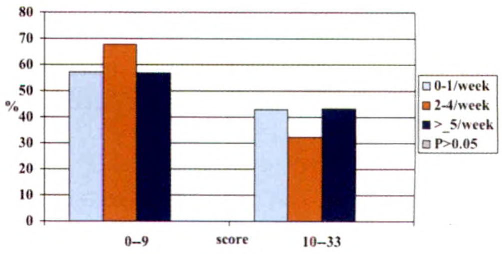

Figure 6. Distribution of women by premenstrual symptoms score and intake of fiber-rich foods.

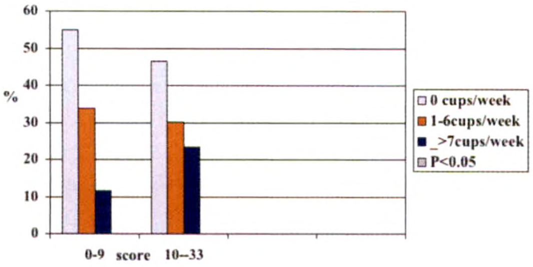

Figure 7. Distribution of women by premenstrual symptom score and intake of coffee.

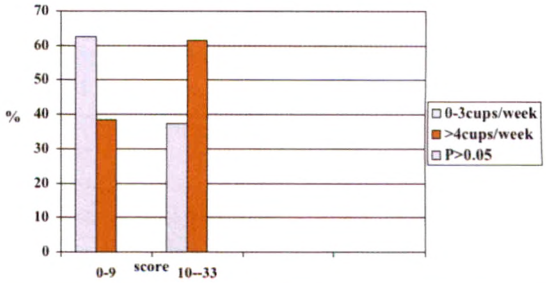

Figure 8. Distribution of women by premenstrual symptom score and intake of cocoa-chocolate drinks.

Discussion

The proportion of women in our study reporting at least one premenstrual symptom during the last six months (96.6%) is in line with several other population-based, retrospective studies conducted in young women. [9,11,13-19] Several series have also reported that premenstrual syndrome is more common among young, urban literate women,[16,20] especially among those involved in professional studies, than older, rural and illiterate women.[20] This may be related to an increased level of perception and reporting of these symptoms in this group. A review of published data on premenstrual syndrome has shown that retrospective, self-report studies[13-19] generally show a much higher prevalence of the condition than in prospective studies linking specific symptoms with the menstrual cycle.[21,22] Though the superiority of prospective versus retrospective studies in diagnosing premenstrual syndrome is established,[23] the inherent difficulties in conducting such research over large samples of population is obvious. What is important to note is that premenstrual syndrome remains a clinical entity of great significance in medical practice due to its common occurrence and its symptomatic polymorphism. In 25-35% of women it is a worrisome problem that requires specialized consultation and in 5-10% it becomes grave due to the extension or seriousness of symptoms.[24] Hence it is necessary to identify women who are functionally affected and manage them so as to improve their quality of life.

Our findings of a significant positive association between premenstrual symptom severity and a history of maternal PMS are similar to those of Freeman et al for women in the USA.[25] Moreover, Wilson et al[26] observed that PMS mother/daughter dyads experienced significantly more and severe luteal phase symptoms compared to non-PMS mother/daughter dyads. Shared biological and/or psychological factors, which may influence expectations and self-perceptions, may explain mother-daughter dyads.[25] Support for a familial connection related to genetic and environmental factors was provided by Kendler et al [27] in a population-based twin study.

Our results agree with other studies showing that perceived stress in daily life influences the occurrence of PMS. [1,28-31] Some women are more vulnerable to stress than others and are more likely to be victims of PMS.[30] Deuster et al[1] observed that PMS was 3.7 times more common in women with perceived stress than in those with no stress. Moreover, Gannon and colleagues[31] found that chronic stress accounted for a significant amount of variance in premenstrual syndrome. According to the biopsychosocial model, predisposition to PMS is realized as a consequence of biological and genetic influences by which attitudes, beliefs, coping styles and social forces interact to stress women.[28] These findings suggest the need for intervention strategies to cope with stress as they may prove to be effective in ameliorating luteal phase symptoms.

There have been anecdotal accounts and unsystematic reports in the past suggesting that women who exercise experience fewer premenstrual symptoms than sedentary women. Recent studies have reported variable results. Deuster et al[1] found that women with PMS were 2.9 times more likely to be physically active than women without PMS. Choi and Salmon[5] found that competitive sportswomen are not protected from deterioration of mood during the premenstrual period unlike other women who exercise frequently and are protected to some extent. Others[32] have reported that the amount (and not the intensity) of aerobic exercise was significantly associated with lower water retention, autonomic reactions and appetite. Aerobic exercise seems to have more beneficial effect on premenstrual symptoms than anaerobic exercise, especially with respect to premenstrual depression.[33] Carefully controlled prospective studies of 3 to 6 months duration have shown that conditioning exercises carried out by either formerly sedentary or marathon runners significantly decreased premenstrual symptoms related to breast, fluid retention, personal stress, depression and anxiety.[6,34] Another study found that the menstrual cycle and physical exercise had an independent effect on the emotional state of women.[35] Our study showed that women with a higher premenstrual symptom score were exercising more than those with lower premenstrual symptom scores, but it is difficult to tell from our data whether exercise was a cause or a response to their symptoms. Further studies are needed locally to see whether women with PMS exercise more regularly than those without PMS because of the belief that exercise is effective in attenuating symptoms.

Our findings of a significant and independent increase in PMS symptoms with intake of sweet-tasting foods are in agreement with the observations of Rossingal and Bonnlander[12] who found this association even when they controlled for beverages high in caffeine content. This points to the need for educating PMS sufferers on curtailing these dietary items. Several studies[9-11,36] have observed a strong association between caffeine and caffeine-containing beverages and PMS. Phillis[37] has suggested that the depressive action of adenosine on central neurons is the mechanism by which caffeine might cause PMS.

Research conducted on medical students[38] and the general population [37] has shown that caffeine in general, causes or exacerbates symptoms of anxiety or depression and increases these symptoms during the premenstrual period.[37] Our study also showed a significant, positive and independent effect on premenstrual symptom severity by total intake of caffeinated beverages in general, and caffeinated coffee and cocoa-chocolate drinks in particular. The observed effects of tea, 'Gahwa' (Arabian coffee) and cola drinks did not reach significant levels possibly due to a lower dose effect of caffeine per cup for these beverages compared to coffee. As per standard values, one cup (5-6 oz) of caffeinated coffee usually has 60-85 mg of caffeine while that for tea and cola drinks is reported to be 20-30 mg and 18 mg[39] per cup, respectively. The caffeine content for "Gahwa," a very mild coffee drink that is popular in the Middle East, has not been reported in the scientific literature. Cocoa drinks may contain 6 to 142 mg of caffeine,[40] depending on the amount of cocoa powder added per cup. Contrary to our findings, Rossingnol and colleagues reported a strong positive relationship between tea consumption and PMS. A possible explanation for this discrepancy is that many of their subjects were tea factory workers who were consuming up to 8 cups of tea per day whereas 97% of our study population drank ≤2 cups of tea per day.

One is often faced with the question of whether women with premenstrual syndrome self-medicate themselves with caffeine in response to symptoms and thereby exacerbate symptoms. While one prospective study [41] investigating the relationship of caffeine intake with PMS found that women do self-medicate themselves with caffeine during the premenstrual period, another case-control study showed no variation in the amount of caffeine consumed in the pre- or post menstrual period.[7] While an association between caffeine intake and PMS is plausible, more studies are required to establish whether caffeine consumption is a cause or a response to PMS. Some authors have suggested that the observed association between caffeine-containing beverages and PMS is that the consumption of these beverages is related to intake of large quantities of fluid, which per se may increase the frequency premenstrual symptoms. One of the limitations of our study is that we did not estimate the effects of total fluid intake on PMS. Others[42] who have studied this relationship have found it difficult to ascertain a causal relationship. It is believed that the mechanism is either related to a perceived increase in fluid retention[42] or instability of vascular regulation in women with PMS.[8]

The multiple regression analysis showed that self-reported mental stress, history of maternal PMS, physical activity, frequent intake of sweet-tasting food items and caffeinated beverages explained only 14% of the variation in the premenstrual symptom score. Various studies have suggested other putative causes: hormonal imbalance, dietary deficiencies,[43] high-fat foods, tobacco use[44] and psycho-social disorders[30,45] none of which were investigated by us. No single theory has been established to explain the entire diversity of PMS symptomatology. More explanatory research is required to unravel the etiological factors of PMS and its pathophysiological mechanism. The findings of the current study could be generalized to young Saudi women who are urban and literate. Our data lend support to the concept that a differential response to daily stresses is an important aspect of the severity of PMS. It would be worthwhile to suggest to women with PMS that they take advantage of the beneficial effects of relaxation techniques and psychotropic therapies.[46] Moreover, as others have also suggested[9-12] women with PMS might also consider eliminating sweet-tasting food items and caffeine-containing beverages, particularly coffee, from their diet.

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NECROTIZING FASCIITIS INDUCED BY SELF-INJECTION OF KEROSENE

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Self-mutilation by means of kerosene injection is a rare occurrence. Only six specific cases of kerosene injection have been reported so far in the literature.[1-3] However, three other cases of chemically induced necrotizing fasciitis, possibly due to kerosene derivatives, have been reported.[4,5] This type of injury is very serious since it has potentially devastating consequences.

Kerosene is available for domestic use in developing countries mainly for cooking purposes. It is primarily a mixture of hydrocarbons. If these hydrocarbons come in contact with the skin surface, they can cause dryness, scaling and sometimes severe dermatitis.[6] When injected under the skin kerosene causes an intense local inflammatory reaction with necrosis of the skin, fatty tissue and possibly underlying muscle.[2, 7]

Burn accidents following explosion or misuse of kerosene, and to a lesser extent poisoning secondary to ingestion, constitute significant emergency admissions.[8, 9] Apart from a few cases of accidental ingestion, most of the cases reported in the literature were self-inflicted with the intention of committing suicide. In the reported cases, the authors advocated aggressive, timely and repeated surgical debridement until reaching viable tissue, followed by possible skin graft.[4] Aggressive and repeated continuous surgical treatment in our case was rewarding in that we avoided amputation.

Case

A 33-year old Iraqi male patient was admitted through the emergency room (ER) of the Northern Area Armed Forces Hospital, King Khalid Military City, Hafr Al-Batin, Kingdom of Saudi Arabia. Following an argument with a colleague, the patient had injected about 5 mL of kerosene on both sides of his right leg four days prior to presentation in the ER. He experienced initially mild pain and redness at the two injection sites. After three days the pain became intolerable with inability to sleep. The right leg became swollen with loss of function. The pain was so severe, despite the administration of a full dose of narcotic analgesic, that he demanded amputation on admission.

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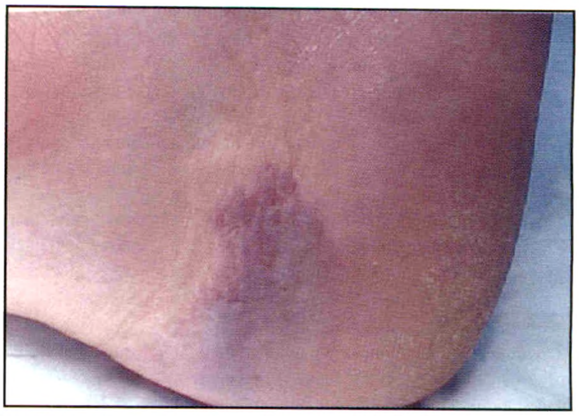

Figure 1. Hemorrhagic ischaemic changes on the lateral aspect of the right heel.

There was nothing significant in his medical history, and he had no psychiatric problems. Clinical examination in the ER showed an ill-looking, but alert patient, well-oriented in time and space. He was in agonizing pain, with a temperature of 38.4 °C, blood pressure 100/65 mmHg, pulse 110/minute and respiratory rate 21/minute. All other systems were essentially normal. Urine output was also satisfactory.

Local examination of the right leg revealed indurated, tender weeping red areas of about 3 by 4 centimeters on both medial and lateral borders at its lower one-third. There was also marked swelling involving the lower half of the leg, and redness of the medial border of the foot with hemorrhagic ischemic changes at the lateral aspect of the right heel (Figure 1). The foot was generally warm, but no capillary refilling of the toes could be elicited. The peripheral pulsations (dorsalis pedis and the posterior tibial arteries) could not be felt. Bedside Doppler stethoscope auscultation of peripheral arteries on admission was not helpful. Plain X-ray films of the right leg and foot did not show any evidence of bony injury or gas in the subcutaneous and fascial planes. Intra-compartmental pressure was not measured. Blood

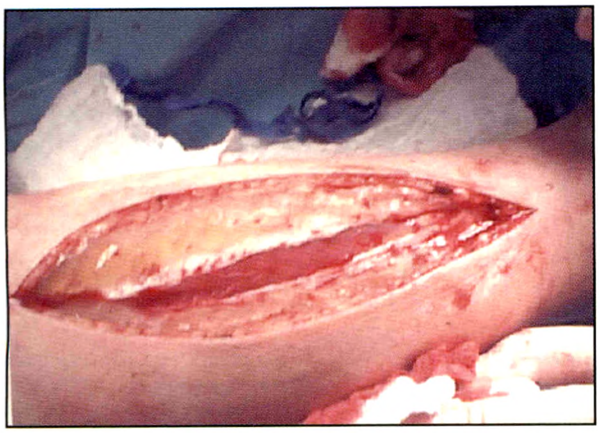

Figure 2. Fasciotomy of the leg, extending to the deep fascial layers.

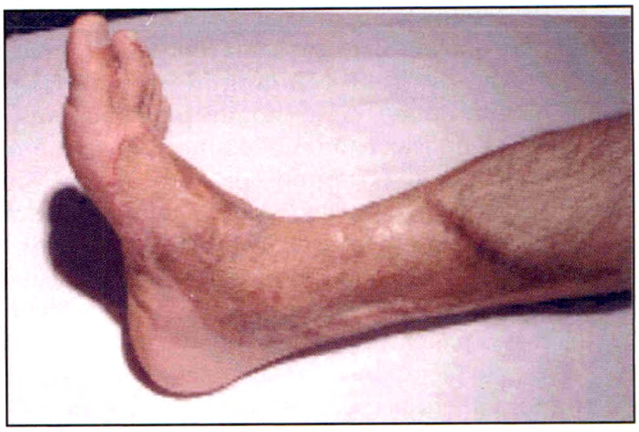

Figure 3. Complete healing of the leg after the skin graft.

count, urine analysis, electrolytes and urea, blood sugar and liver function tests during admission were within normal limits. Blood culture was negative.

We made a provisional diagnosis of self-inflicted acute necrotizing fasciitis with compromised venous return secondary to injection of kerosene. Immediate management included admission to the ward, commencement of broad-spectrum antibiotics, and elevation of the right lower limb. Within two hours of admission the patient was taken to the operating room (OR) where he had multiple fasciotomies extending to the deep fascial layers of his right lower limb (Figure 2). The kerosene smell was very characteristic after cutting into the subcutaneous layer, and the operating field was obviously ischemic.

Swabs were taken for culture and sensitivity, which were negative. There was obvious improvement in the capillary refill of the toes after the fasciotomies. Dressing was then applied and pulse oximetery showed oxygen saturation of 97%. Repeated sessions of wound debridement with removal of devitalized skin and subcutaneous tissues were carried out with repeated wound swabs, all of which proved negative. He was referred to the psychiatrist in view of the emotional circumstances that led to the injury and was diagnosed as suffering from personality disorder.

Histopathology specimens sent at the time of the initial surgical debridement showed a massive, variable acute inflammation, with aggregation of neutrophils, and focal fat necrosis with hemorrhage. Further wound debridement continued until the necrotizing process gradually ceased and healthy granulation tissue appeared. Skin grafts were applied later with subsequent complete wound healing (Figure 3) after which he was discharged from the hospital.

Four weeks after discharge from the hospital the patient re-injected himself in the same limb with kerosene, but he presented at our hospital this time within 24 hours. His reason for mutilating the same limb again was that he had not been allowed to attend follow up in the hospital. He suffered moderate cellulitis for which he was treated with incision and decompression followed by a few sessions of wound debridement. On this occasion no necrosis occurred and delayed primary wound closure was carried out with no complications. The patient was followed up for eight months without any serious problems with his wound.

Discussion

Self-injection with kerosene is a rare but serious injury. In reviewing the clinical picture of this case, time was an important factor. Delay in management would have allowed the noxious agent to cause much irreversible necrosis and possible suppuration.[4, 9] Since the injected material penetrates slowly, immediate and adequate surgical debridement with possible fasciotomy is the best initial treatment, followed by repeated and relentless debridement with dressings. Systemic effects may accompany the local disturbance, which is usually characterized by fever, leucocytosis and lymphangitis. For this reason, antibiotics should be given to protect against staphylococcus, the most likely offending microorganism in these cases. Treatment may be changed as required when culture results become available.

The psychiatrist diagnosed the patient as having personality disorder, which we tended to agree with. The patient confessed to being frustrated because he was a college graduate with no hope of progress.[10,11]

Apart from injecting himself twice with kerosene, he continued to mutilate this same limb by continuously scratching the graft, resulting in frequent hospital visits. In addition, eight months after final hospital discharge he was re-admitted after ingesting broken razor blades wrapped in paper. This was conservatively managed and all ingested metallic pieces were passed after three days without any residual effects. The most common injury in patients with personality disorder is wrist cutting. Mentally disturbed patients have been known to inject milk or faeces into themselves, inducing severe cellulitis. This type of patient needs continuous psychiatric follow-up and a solution for their social frustration.

Self-injections of kerosene are rare, unusual and can produce severe tissue damage, especially if prompt surgical treatment is delayed. We therefore suggest that active and immediate surgical intervention in the form of complete multiple fasciotomies, incision and surgical excision of non-viable tissue be instituted as soon as possible. It should also be followed by active and repeated aggressive wound debridement until healthy granulation tissue is encountered. Usually the area of destruction inflicted by the kerosene is wide, and it will invariably need skin grafting later. Skin grafting is the only option available to salvage the jeopardized limb. Psychotherapy is also an integral part of the management.

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MENINGEAL CARCINOMATOSIS: A RARE CAUSE OF CAUDA EQUINA SYNDROME

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Intramedullary and meningeal metastasis to the spinal cord from distant malignant tumors is rare. The commonest tumor to metastasize in this fashion is lung cancer, accounting for around 50% of cases.[1,2] The incidence is on the increase since cancer patients are living longer and techniques of diagnosis are getting better.[3] Cauda equina syndrome (CES) has been described as a complex of low back pain, bilateral sciatica, saddle anesthesia, and motor weakness in the lower extremities that may progress to paraplegia with bowel and bladder incontinence.[4] Orthopedic surgeons in general see only a few cases of CAS in their working career. The vast majority are produced by central disc herniation in the lumbosacral area. We present a case of meningeal carcinomatosis producing the classic picture of CES.

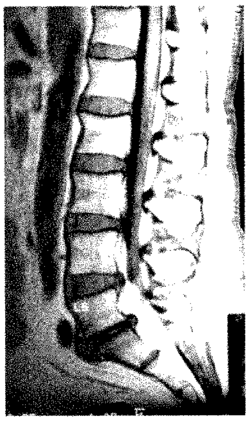

Figure 1. MRI of the lumbo-sacral spine in 58-year-old male patient.

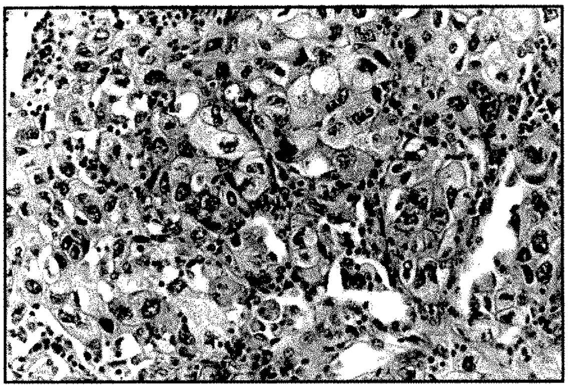

Figure 2. Pathology of resected lung tumor showing adenocarcinoma of the lung, poorly differentiated.

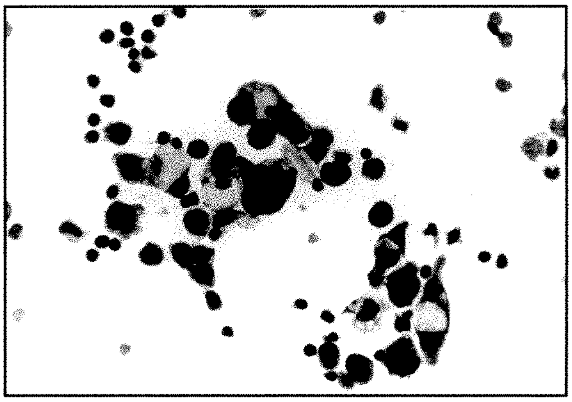

Figure 3. Cerebrospinal fluid containing malignant epithelial cells with many cytoplasmic vacuoles, consistent with metastatic adenocarcinoma (Papanicolau, 40 x)

Case

A 58-year-old male patient presented to a private clinic with a two-month history of progressive sensory loss in the perianal area and gross weakness of the dorsiflexors and plantaflexors of the right ankle. Three MRIs of the lumbo-sacral spine, the last performed on admission to American University Hospital (Figure 1), were normal.

His medical history was significant for a 8 x 6 x 6 centimeter mass in the upper lobe of the right lung discovered on a routine chest x-ray in September 1993. He was found to have a poorly differentiated primary adenocarcinoma of the lung with a free surgical margin (Figure 2). None of the removed peribronchial lymph nodes showed evidence of disease. No chemotherapy or radiotherapy was given to the patient.

Physical examination on the present admission revealed saddle hypoesthesia with a weak anal tine. He had Grade 4/5 MRC scale motor power of the plantarflexors and dorsiflexors of the right ankle. The rest of the exam was normal. EMG revealed evidence of bilateral L5 and S1 root pathology. The metastatic workup, including CT scans of the chest, abdomen and pelvis

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were normal. A 99m TC bone scan revealed two suspicious foci in the skull. Routine blood tests were normal.

The lumbar puncture revealed the presence of adenocarcinoma cells (Figure 3). We made a diagnosis of meningeal carcinomatosis as a cause of CES, and the patient was referred to the oncology service for further management.

Discussion

Meningeal carcinomatosis is defined as a spreading of tumor cells throughout the meninges and ventricles. Although metastasis to the central nervous system is found in 25% of tumors, spread to the spinal meninges and cord is rare (2.1%).[2] About 1.65% of lung tumors metastasize to the cord.[6] According to Hiroaki et al,[6] 157 cases of spinal metastasis have been reported in the English literature. In their study 20 of 1215 autopsies of lung cancer showed evidence of meningeal metastasis. Lung cancer accounts for 56.5% and breast cancer for 13.6% of the metastases. However malignant melanoma, lymphoma, rectal cancer, head and neck cancer have been reported.

Meningeal metastasis can occur by hematogenous spread, which accounts for most cases. Hematogenous spread can occur through an arterial route [2] or through the vertebral venous plexus with retrograde spread to the spinal cord.[1,7] Another route is by meningeal carcinomatosis, with tumor cells infiltrating the Virchow-Robin spaces of the vessels going to the spinal cord.[1,7] A third mechanism is direct invasion from contiguous structures through direct extension from the extradural space or CSF, or by means of nerve roots through the dura into the spinal cord.[5] Interestingly, metastasis is not distributed evenly along the spinal cord. It is more common in the lumbar spine.[6]

Gadolinium enhanced MRI is very helpful in the diagnosis of meningeal carcinomatosis and is positive in up to 66 % of cases.[8] It may show abnormal enhancement or nodularity of the leptomeninges or hydrocephalus.[9] It is also helpful in ruling out the presence of disc herniation as a cause of CES. Myelography is highly correlated with the clinical diagnosis of CES with no false negative results. Myelography may show nodular filling of the subarachnoid space, and thickening and crowding of the route of the cauda equina, irregularity of individual roots, and scalloping of the subarachnoid membranes. MRI is rather insensitive in detecting these changes, revealing a definitive abnormality of the subarachnoid space in 27% of patients with a positive myelogram.[10]

The cornerstone of the diagnosis is the cytological examination of the CSF fluid. The sensitivity of a single CSF examination is approximately 60%.[11] This increases to 75% with two examinations, to 85% with three examinations,[7] and to about 95% after multiple taps.[8] It is therefore advisable to repeat the test when there is a high index of suspicion and the first taps are negative.[12] In our case, the patient presented with a typical history and findings of CES. The MRI failed to show any pathology that could explain his symptoms.

In view of the history of resected lung cancer five years ago, the CSF cytologic examination was performed and turned out positive. It is known that meningeal carcinomatosis is a late complication of lung cancer in 10% of patients.[13] Fifty-two percent of lung cancer patients have a neurologic complication at the time of diagnosis.[13] CES may be an isolated presentation of meningeal carcinomatosis.[9]

The prognosis is poor. In a study by Nakagawa, 22 of 29 patients showed symptomatic improvement with intrathecal methotrexate alone or combined with cystosine arabinoside with or without radiation. In 33 patients treated with radiation, intravenous chemotherapy and intrathecal chemotherapy, symptoms improved in 15% of patients with a median survival of only nine weeks.[6] In that study, patients with primary breast cancer did better than those with primary lung cancer. In general survival is poor despite aggressive treatment. In our case, CES as a manifestation of meningeal carcinomatosis occurred five years later despite the favorable prognosis at the time of initial treatment. In conclusion, not every CES is a disc herniation in need of surgery. A CSF study should be performed even in the presence of a normal MRI.

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DIABETIC MUSCLE INFARCTION – AN OFTEN MISSED COMPLICATION

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Diabetic muscle infarction (DMI), or myonecrosis, is an uncommon and often missed complication of diabetes. It occurs in both types of diabetes, but more often in type 1 and appears to be attributable to microangiopathy. It has a characteristic clinical presentation, including acute onset of painful swelling most commonly in the thigh or calf muscles in the absence of systemic manifestation. It is frequently misdiagnosed clinically as neoplasm, abscess, focal myositis, or deep vein thrombosis. Magnetic resonance imaging (MRI) is extremely helpful in making the diagnosis and excluding other possibilities. It usually improves gradually to complete resolution within weeks to a few months. The two cases described emphasize the importance of early recognition and diagnosis of this complication to avoid an unnecessary intervention or hazardous treatment.

Case

Case 1. A 62-year-old female patient presented with a three-day history of pain and swelling of the left leg, which had gradually increased over the last 24 hours prior to admission. There was no history of trauma, fever or previous history of similar episodes. She had had diabetes mellitus type 2 for 22 years and had been on insulin therapy for the last 5 years. She also had had hypertension for 4 years and had developed diabetic nephropathy 2 years ago. On physical examination the left calf muscle was swollen and tender, but the foot was neither swollen nor tender. A presumptive diagnosis of deep vein thrombosis (DVT) was made and she was treated with heparin. Laboratory investigation revealed WBCs of 10,700/mm^3 with 85% granulocytes, creatinine 2.4 mg/dL, and creatinine kinase 340 IU/L (normal up to 170 IU/L). Doppler ultrasound of the calf, done on the next day, showed edema of the gastrocnemius muscle with no evidence of DVT. Arterial Doppler study showed significant obstruction of the anterior tibial artery. MRI of the legs (Figure 1) showed swelling and high signal intensity in T2-weighted images in the left gastrocnemius and soleus muscles with subcutaneous edema. A diagnosis of DMI was made. Heparin was replaced by analgesics and the patient was advised to rest in bed. The swelling subsided significantly within 4 weeks and almost returned to normal after 8 weeks with disappearance of the pain.

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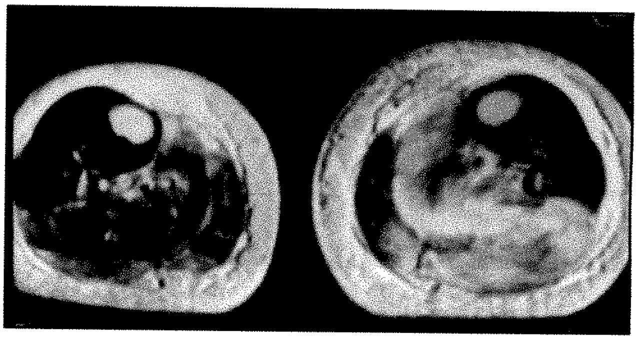

Figure 1. T2-weighted sequence MRI of the calf muscles showing swelling and high signal intensity of the left gastrocnemius and soleus muscles with subcutaneous edema.

Case 2. A 52-year-old male patient who had had type 2 diabetes mellitus for 18 years was admitted in April 2001 with a history of pain and swelling of the upper right thigh of 3 days duration. His previous medical history included myocardial infarction in 1998 and he had developed peripheral neuropathy in 1991. In July 1992 he presented with a one-day history of a large painful swelling in the proximal part of the right thigh. The swelling was firm and tender but not fluctuating or pulsating. An MRI of the right thigh (not available) was reported as a large mass infiltrating the adductor muscle. Needle biopsy gave 20 mL of serosanguinous fluid, the histology of which showed necrotic tissues and muscle fibers. Bacteriologic culture of the fluid was negative. No diagnosis could be reached at that time; therefore surgical excision of the affected muscle was done. Histology showed non-specific inflammatory reaction in the affected muscle with necrosis and intramuscular hemorrhage (Figure 2). Physical examination showed very tender swelling of the medial aspect of the right thigh extending from theinguinal ligament to the lower part of the thigh. Signs of peripheral neuropathy were also present.

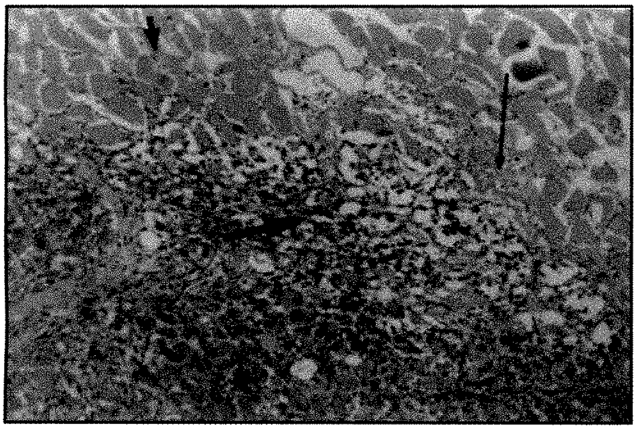

Figure 2. Histological section of the excised muscles showing normal muscle fibers (thick, short arrow), areas of muscle fiber degenerations and interstitial infiltration (thick, long arrow) and area of hemorrhage (thin, long arrow).

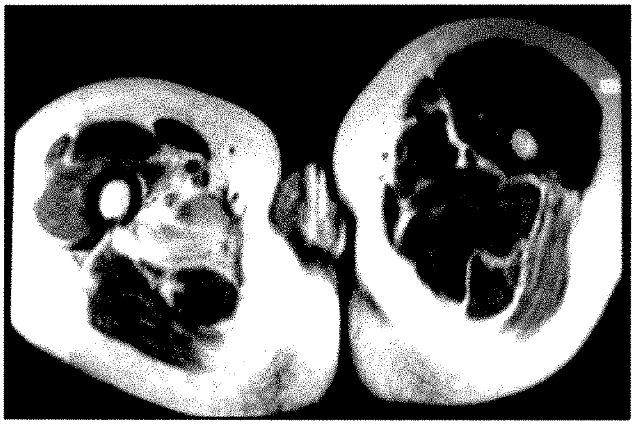

Figure 3. T2-weighted sequence MRI transverse images of the upper thighs showing reduction in size of the adductor muscles (due to previous surgery) and high signal intensity in the same muscles (arrow).

Needle aspiration of the thigh revealed necrotic tissue with muscle fibers. MRI (Figure 3) showed a marked reduction in the size of the adductor (secondary to a previous partial resection) with edema and high signal intensity in the remaining adductor muscles. On the basis of previous and current data, a diagnosis of DMI was made. The patient was put to rest with adequate analgesics. The pain and swelling subsided gradually over the next three months of follow up.

Discussion

Angervall and Stener first described diabetic muscle infarction in 1969.[1] They described two diabetic patients who had excision of a painful thigh mass, which was suspected of benign soft tissue tumors. Histologically they found areas of hemorrhagic necrosis surrounded by muscle that showed degenerative changes and evidence of regeneration. They called it tumoriform focal muscular degeneration. Since then, considerable experience has accumulated through case reports and review of previously published cases.[2-14] Diabetic muscle infarction is a distinct entity with characteristic clinical and radiological findings. It is probably more common than previously recognized.[2] The two cases presented illustrate the clinical presentation of this complication. Typically the patient presents with a painful mass in the thigh or calf muscles, and with localized swelling and tenderness on examination. The onset is usually acute, and spontaneously resolves after several weeks to months.[3]

Recurrent episodes of muscle infarction in the same or a contralateral limb are reported to occur in half of patients, some of whom may have multiple recurrences.[4,5] The second patient developed a second attack nine years after the first in the same group of muscles. DMI usually occurs in a patient with long-standing diabetes, with a mean duration of 15.8 years before the occurrence of DMI.[5] Patients with type 1 diabetes outnumber those with type 2. Lower limbs and particularly the thigh muscle are the site of presentation in 90% of cases with the calf muscles being the next most frequent.[5,6]

The cause of diabetic muscle infarction appears to be diabetic microvascular disease since the majority of patients have multiple microvascular complications.[6,7,8] In a review of reported cases before 1996, Umpierez et al [8] found a number of risk factors for this complication, including poor diabetic control and microvascular complications (nephropathy, retinopathy, or peripheral neuropathy) in 94% of patients, insulin-dependent diabetes in 77%, and presentation with painful diffuse muscle swelling in 100%.

Failure to recognize this complication usually results in extensive testing and sometimes in unnecessary surgery, as occurred in the second case, and sometimes in unnecessary or hazardous therapy, as in our first case. MRI is extremely helpful in establishing the diagnosis and extent of the infarction.[9,10] The typical finding is high signal intensity with diffuse enlargement of the involved muscle group and sometimes extensive subcutaneous edema. This is best demonstrated on T2-weighted, inversion-recovery and a gadolinium-enhancedsequence.[5,12] Histological features of DMI consist of a large area of muscle necrosis and edema. Regeneration of the muscle fibers, and polymorphonuclear and lymphocytic interstitial infiltrates may be present. [9,10]

Management consists of resting the muscles, analgesics and gradual mobilization. In most cases symptoms will resolve spontaneously within a few weeks to a few months with improved diabetic care and supportive measures.[5] However, some patients may not improve with conservative therapy and may need surgical resection of the muscle. Aboulafia[7] reported that two of his 14 patients improved only after resection of the involved muscle. Occasionally fasciotomy may be required if muscle edema has compromised the neurovascular integrity, resulting in compartment syndrome.[13]

The short-term prognosis for DMI is excellent because symptoms resolve spontaneously in a period of several weeks to months. However, the long-term prognosis is grave since the majority of patients die within five years of diagnosis due to the severity of diabetic complications.[9,14] Awareness of diabetic muscle infarction by the internist, diabetologist, rheumatologist and the orthopedic surgeon should allow early diagnosis on the basis of clinical presentation and MRI findings, thereby avoiding unnecessary investigations and medical and surgical intervention.

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ERYTHROMELANOSIS FOLLICULARIS FACIEI: FIRST CASE REPORT FROM SAUDI ARABIA

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Erythromelanosis follicularis faciei (or erythromelanosis follicularis faciei et colli when the neck is also affected) is a rarely documented skin disease. In this paper, a case of erythromelanosis follicularis faciei in a Saudi male patient is presented. We believe it is the first case from Saudi Arabia.

Case

A 17-year-old Saudi male was referred to the dermatology department, King Fahd Hospital of the University, Alkhobar, Saudi Arabia, for evaluation of asymptomatic red lesions on the face. The duration of the lesion was six years. The cheeks were initially involved and the lesion gradually expanded. Exposure to sun aggravated the lesion. There were no systemic complaints and the family history was negative for similar lesions. The examination revealed well-defined symmetrical red-brown lesions with follicular papules involving the cheeks, lower lip and auricles (Figure 1). Beard hair on the cheeks was decreased. Keratosis pilaris was present in the shoulder areas. ANA and anti-double strand DNA were negative and the erythrocyte sedimentation rate and complete blood count were within normal limits. Biopsy showed mild hyperkeratosis, follicular plugging and increased pigmentation of the basal layer (Figure 2). In the dermis, there were dilated blood vessels and a sparse perivascular lymphocytic infiltrate.

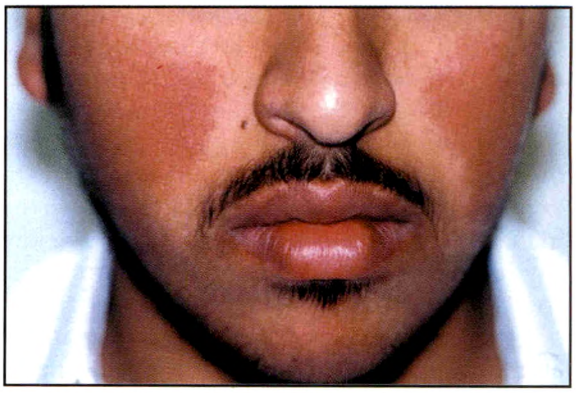

Figure 1. Well-defined symmetrical red-brown lesions with follicular papules in a 17-year old Saudi male with erythromelanosis follicularis faciei.

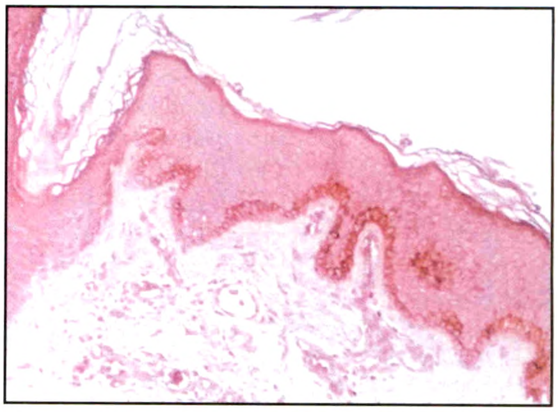

Figure 2. Biopsy showing mild hyperkeratosis, follicular plugging and increased pigmentation of the basal layer.

Discussion

Erythromelanosis follicularis faciei was first described in Japanese males by Kitumura et al. 1960.[1] A few more cases have been reported from different parts of the world, but the total number of reported cases worldwide is only about a hundred.[1,19] The clinical appearance consisted of sharply demarcated patches of erythema, hyperpigmentation and follicular plugging with or without telangiectasia.[1,19] The cheeks and periauricular area were commonly involved with extension of lesions to the side of neck. Involvement of the auricle and eyebrows has been regarded as unique and atypical[9,10] but in a recent report from Iran, it was common.[18] Diminished hair in the affected sites has been observed.[2,4,18] The lesions were mostly symmetrical but unilateral cases have been reported.[5,11] Most of the patients had keratosis pilaris on the limbs. The age of onset in the majority of cases was in the first and second decade and both sexes were affected.

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The etiology of erythromelanosis follicularis faciei is not known. A possible autosomal recessive mode of inheritance and a polyetiology, i.e. familial and environmental, have been suggested.[13,19] Autonomic nerve dysfunction has been proposed.[2] Cold, heat, exercise, emotional upset and exposure to the sun were reported as aggravating factors.[15,18] The reported histopathological findings are not diagnostic, but correlate with the clinical picture.[20] They included hyperketosis, follicular plugging, excessive melanization and dilated blood vessels with inconspicuous lymphocytic infiltrate. Deposits of calcium in the upper dermis were found.[21]

Erythromelanosis follicularis faciei should be considered in the differential diagnosis of the facial melanosis and disorders of keratosis pilaris atrophicans, particularly ulerythema ophrogenes of Taenzer and keratosis rubra pilaris facie atrophicans of Brocq. Erythrosis pigmentosa perbuccalis and erythromelanosis follicularis faciei have been reported in the same patient and were regarded to be identical. Erythromelanosis follicularis faciei runs a progressive course. Some improvement with topical applications of tretinoin or its combination with hydroquinone and ammonium lactate and metronidazole have been reported.[4,5,11,16]

The clinical and histopathological features of the case presented here are identical to those reported in the literature with the exception of the involvement of the auricles and lip. It seems too early to regard lip pr, as has been mentioned above, auricular involvement atypical because of the few cases reported so far. To conclude, it is important to formally document this case of erythromelanosis follicularis faciei in our local medical literature in the event that it is more widespread and to avoid confusion with other differential diagnoses.

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QUALITY OF LIFE PERCEPTIONS OF HOSPITALIZED PATIENTS

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The WHO definition of health includes not just the absence of illness but also a complete state of physical, social, and mental wellness.[1] The increasingly mechanistic and technical model of medicine, concerned only with eradication of disease and symptoms, reinforces the need to introduce a humanistic element into health care. Quality of life (QOL) is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[2]

This article focuses on health-related quality of life in adult patients with various chronic diseases who were hospitalized in internal medicine wards for at least two weeks. We used the WHOQOL-TR, the Turkish version of the WHOQOL-100.[3]

Patients and Methods

Research was carried out with adult patients who were hospitalized for at least 2 weeks in the clinics of the Internal Medicine Department of the Istanbul Medical Faculty between October 1999 and June 2000. Out of 145 patients recruited for the study, 24 dropped out for clinical or other reasons and 22 failed to provide adequate data and were excluded. A total of 99 patients with various diseases, mostly chronic, were included.

WHOQOL is a generic QOL instrument, which was developed through an international collaboration of 15 simultaneously involved field centers. The aim was to develop a QOL assessment that would be applicable cross-culturally.[2] We used a local version of WHOQOL-100, which had 103 items and 7 domains and with good test-retest reliability, and construct, discriminate and criterion/concurrent validity. Scores ranged from 1-100. High scores indicate good QOL.[3] The questionnaire consisted of social and demographic variables (age, gender, marital status, education, personal belief), hospitalization-related variables (duration, frequency), disease variables (diagnosis, duration), and symptom information. We used t-tests and one-way analyses of variances (ANOVA) to assess significant differences across groups.

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Results

The mean (±SD) age of the 99 patients was 41±17 years (15-79 years). Women (mean age 40±14) formed the largest group (n=62, 62.6%). The mean age of the men (n=36, 37.4%) was 42±18 years. 37.8% of male patients were single, 54.1% were married, and 8.1% were widowed; 33% of female patients were single, 48% were married, and 19% were widowed. The mean duration of sickness was 75±90 months (ranging from 1 to 360 months), and the mean duration of hospitalization was 4.1±2.9 weeks (ranging from 2 to 18 weeks).

The social pressure domain had the highest score (71±22) of the QOL domains (Table 1). Spirituality/religion/personal belief was the least affected domain followed by social relationships, environment and level of independence. The physical domain had the worst scores (47±18) (Table 1). Personal relationships were the least affected facet, although mobility, dependence on medical substances and medical aid and energy facets were the most affected ones (Table 2).

Women had lower levels of QOL in all domains and facets compared with men. Men had significantly better scores at facets of sleep and rest, bodily image and appearance, personal relationships, physical freedom, physical safety and security, home environment ($P<0.05$), health and social care (accessibility and quality) ($P<0.01$), and all domains of social relationships and environment ($P<0.05$).

Higher age correlated negatively several facets (Table 2), including energy, sleep and rest ($P<0.001$), mobility, activities of daily living, work capacity ($P<0.01$), positive feelings, thinking, learning, memory and concentration, opportunities for acquiring new information and skills ($P<0.05$), and the domains of physical health, level of independence ($P<0.001$), and social relationships and psychological health ($P<0.05$) (Table 1). Dependence on medicinal substances and medical aids increased with age ($P<0.01$). Married people reported better satisfaction on the positive feelings facet and physical health domain, compared to unmarried, divorced or widowed people, whereas single patients had better scores on the energy facet ($P0.05$). Social support decreased with the duration of hospitalization ($P<0.05$).

Overall QOL and health status ranged from '1' (very poor) to '5' (very good). Women (2.38±1.09) had worse

Table 1. The mean domain scores of WHOQOL.

Domain	QOL score (mean ± SD)
Social Pressure	71 ± 22
Spirituality, Religion and Personal Belief	66 ± 21
Social Relationships	63 ± 16
Psychological Health	61 ± 14
Environment	57 ± 15
Level of Independence	50 ± 20
Physical Health	47 ± 18

Table 2. The mean facet scores of WHOQOL.

Facet	QOL score (mean ± SD)
Personal relationships	71 ± 20
Home environment	71 ± 23
Bodily image and appearance	69 ± 20
Self-esteem	67 ± 21
Social support	64 ± 20
Positive feelings	63 ± 20
Thinking, learning, memory, and concentration	63 ± 19
Physical safety	61 ± 20
Transport	59 ± 25
Opportunities for acquiring new information and skills	57 ± 21
Pain snd discomfort	56 ± 21
Sleep and rest	56 ± 27
Negative feelings	56 ± 22
Health and social care: accessibility and quality	55 ± 24
Overall QOL and health status	54 ± 22
Financial resources	53 ± 21
Work capacity	52 ± 31
Sexual life	52 ± 24
Participation in and opportunities for recreation and leisure	52 ± 23
Activities of daily living	51 ± 22
Physical safety	48 ± 20
Mobility	44 ± 24
Dependence on medicinal substances and medical aids	43 ± 28
Energy and fatigue	41 ± 21

perceived overall QOL and health status than men (2.86±0.9) (P=0.02). Pain and discomfort, dependence on medicinal substances and medical aids ($P<0.001$), and negative feelings ($P<0.05$) all had a negative correlation with overall QOL and health status. A significant positive correlation was found with energy, sleep and rest, mobility, activities of daily life, work capacity, participation in and opportunities for recreation/leisure ($P<0.001$), thinking, learning, memory and concentration, self-esteem ($P<0.01$), positive feelings, sexual life, physical environment, and opportunities for acquiring new information and skills ($P<0.05$). Overall QOL and health status had a positive correlation with physical health, psychological health and level of independence domains ($P<0.001$), as well as social relationships and environment ($P<0.05$).

Patients with heart diseases had worse sleep and rest ($P=0.01$) scores but had better scores on personal relationships ($P<0.05$) compared with the rest of the study group. In general, work capacity was better for patients who didn't have cancer ($P=0.01$). Diabetics had significantly high scores on dependency on medicinal substances and medical aids ($P<0.001$); and positive feelings and opportunities for acquiring new information and skills ($P<0.05$). Diabetics had lower scores across all domains but only social relationships and level of independence had significantly low scores ($P<0.05$). Patients who had infectious diseases had lower scores than others in the domains of psychological health, environment ($P<0.05$), level of independence ($P<0.01$) and facets of positive feelings ($P<0.01$), self-esteem, mobility, work capacity ($P<0.05$), opportunities for acquiring new information and skills ($P=0.005$) and overall QOL and health status ($P=0.005$). Patients who had psychological problems had bad scores in the domains of social relationships ($P=0.01$) and social pressure ($P<0.05$). Patients who had only one disease had better physical health, and opportunities for new information and skills ($P<0.01$), than those who had more than one.

Pain negatively correlated with overall QOL and health status ($P<0.05$). Sleep and rest ($P<0.01$) and financial recourses ($P=0.003$) facets and the domain of physical health ($P<0.05$) had worse scores than patients with more than one symptom.

Discussion

Social pressure as a national item had the highest scores among all patients. During the fieldwork, Fidaner et al[3] found there was a need for this item. Social pressure had a relatively low correlation with other parts of the instrument. Fletcher at al[4] observed that social pressure had increased with illnesses.

The least affected domain among our subjects was spiritual/religion/personal beliefs. Patients who had religious beliefs reported having more hope for recovery, and emotional comfort was stronger. Their confidence in the future, peacefulness, productivity and general satisfaction with life were better.[5] Destiny and faith has an important place in Turkish Islamic culture and this might have an effect on patient coping with illness.

Physical health had the worst scores among all patients in general. Research conducted on diabetic patients showed that physical and social functions are the most affected domains.[6] Bergner[7] reports that physical impairment occurs or increases with age and that has a negative effect on emotional satisfaction and general satisfaction with life. A QOL evaluation with WHOQOL-100 in patients with HIV-1 infection revealed that age had a significant negative impact on the social relationship domain.[8] On the other hand, life satisfaction was found to be increased among patients over 65 years of age with chronic kidney failure.[9] Women had worse QOL than men among all domains and facets of our study. Although Fidaner et al,[3] the WHOQOL Group in Turkey, found that gender had no significant correlation with QOL, other research conducted on diabetic patients using SF-36 reported that women had low scores on energy and mental health.[10] Some researchers suggest that the low QOL scores of women could be due to not only disease but to the reaction to disease.[11] One of the reasons women have more tendency to depression is their more frequent exposure to negative aspects of life than men.[12] In Turkey, most women don't have economic freedom or an outside job, and their life is limited to the domestic environment. They tend to be separated from outside society and have low education levels.[13] The authors think that the socioeconomic and cultural status of women in Turkey might have an negative impact on general satisfaction with QOL.

With the evaluation of overall QOL and health status, 81% of our subjects reported very poor, poor or neither poor nor good. The literature shows a strong positive correlation between overall QOL and health status and the rest of the instrument.[3,14,15] Taking this into account we could say that the vast majority of inpatients didn't have good QOL. Patients with heart disease had significantly lower scores on the sleep and rest facet compared with the patients without heart disease. Although it is not specific to diseases, sleep disturbances are thought to be an alarming aspect of disease severity.[16] Skevington[17] stressed the importance of sleep and rest by including it in most of the frequently affected parameters of QOL with pain. Skevington[17] examined the impact of pain on QOL and found that pain and discomfort made a significant impact on perceptions of general QOL related to health. The QOL scores were the lowest in the patients who had the highest pain levels.

We conclude that the satisfaction of overall QOL and health status was low among hospitalized patients, particularly in women. Activity related facets like mobility and energy were found to be the worst of all facets. The physical domain had the lowest scores. We, therefore, believe that it is essential to determine which aspects of QOL for hospitalized patients have deteriorated and to what extent. It is possible to evaluate their requirements in order to provide multidimensional health care.

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CANNABIS USE IN SHIRAZ, IRAN

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The Islamic Revolution in 1979 was much more than the replacement of the Shah's government by a religiously led government. Virtually every aspect of public life was affected. Many policies of the previous administration were altered or even reversed because they were considered un-Islamic, and drug policy was not immune from such changes. The organization previously in charge of drug treatment, the National Iranian Society for the Rehabilitation of the Disabled, ceased to exist.

Immediately after the revolution, attempts were made to limit cultivation and distribution. During the early months of 1980, the campaign became much stricter, with extensive use of the death penalty for drug trafficking. The new regime also made alcohol a prime target and launched a new national campaign against drug abuse.

Two studies from this period indicate the nature of the problem at this early stage of the revolution. Dalvand interviewed two hundred newly registered addicts at the rehabilitation center in the major provincial capital of Shiraz,[1] and Agahi surveyed a sample of the adolescents of Isfahan.[2] The first study showed that rehabilitation clinics experienced a broader social range of addicts after the revolution than before and that action by the authorities was bringing many recently addicted individuals to clinics. Heroin use predominated among urban residents, whereas villagers were more likely to be opium users.

One aspect of the pattern that would seem to have remained stable in Iran during the years since the revolution was the age of initiation. Nearly 80% of the sample, whether recent or long-term users, had started to use drugs regularly in their 20s or later, whereas in many western studies the percentage of late starters is much lower.[3] In another survey of the adult population, 11% claimed to have used an illicit drug at least once.

Use of opium predominated, with hashish and heroin the only other two drugs mentioned.[2] Among drug-experimenting adolescents, drug use did not seem to be associated with social deprivation as drug users were not over-represented among those from the most deprived social backgrounds. Nor was it an expression of an adolescent counterculture as most young drug users had been introduced to the drug within a family setting rather than as a result of encouragement from peers.[4] Cigarette use, in contrast, was predicted more by peer than family smoking patterns.[3]

There are few other empirical studies in Iran. We have only official press announcements on the extent and success of the campaign on illicit drug use. The country's economy and social order have been considerably affected by the war with Iraq and one can surmise that the drug program has been as much affected as most other aspects of life in the country. Therefore, Iran urgently requires baseline data on substance use to provide guidance for policy making on prevention, treatment, and education.

Little is known about substance dependence in Iran. Iranian drug policy states that the penalties for possession and use of illegal substances are usually arrest and imprisonment. Alcohol is both religiously and legally prohibited. Illicit substances used in Iran include cannabis, heroin, opium, alcohol, stimulants, LSD, and hallucinogens.

The majority of the Iranian population is younger than 25 years (about 60%) and a large proportion of these are students. In a study of the rate of substance use in Iranian senior high school students, 14 % of boys reported using cigarettes and 5.7% were currently using other substances.[5] In a research report about substance abuse among Iranian university students, 24% of the students reported using a substance at sometime in their lives. The rate of substance use is more common in men than women.[6] This paper assessed the prevalence of cannabis use in Shiraz, Iran.

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Methods

As a sample intended to represent the general urban population in Shiraz, Iran, we selected 1500 subjects (men and women) on a multi-stage probability sample of people aged 15 years and older, from Shiraz city, the capital of the Fars province, with a population of about

1.5 million. The subjects were chosen by area and cluster random sampling. We divided Shiraz city into 15 geographic areas. One cluster (each cluster included 100 subjects) was selected randomly from each area. Fifteen clusters were selected from different regions in Shiraz to have a sample representing different socioeconomic status. Of the 1500 subjects, we excluded 100 subjects due to incomplete questionnaires or lack of participation. The overall response rate was 93.3% with 1400 participants (700 men and women).

The data were collected from 1400 subjects using a semi-structured interview and a structured interview based on DSM-IV and ICD-10 criteria for cannabis abuse and dependence, carried out by the authors. A short explanation of the reasons for the study and an assurance of confidentiality were given. The items selected for use in the pilot study were based on DSM-IV, ICD-10, and a prior study.[7]

Face-to-face interviews were conducted in the houses of the subjects. The semi-structured interview included a number of questions, including whether or not they used cannabis in the part or currently. Demographic information was also collected (age, gender, marital status of the subjects). The research also intended to identify reasons (habit, need to avoid withdrawal symptoms, pleasure, tension, depression, other) for cannabis use.

Data analysis was carried out using the SPSS program. The chi-square test was used to test the frequencies and the t test was used for comparing the means. The tests were 2-tailed and the *P*-value was considered significant at the level of 0.05.

Results

Of the participants, 50% (n=700) were men (mean age, 34.61±14.06 years, range, 15 to 80 years) and 50% (n=700) were women (mean age, 30.99±12.90 years, range, 15 to 83 years) ($P<0.001$). The majority (35.9%) were 15 to 24 years old, while 27.4% were 25 to 34 years old, 17.6% were 35 to 44 years old and only 3.9% were older than 65 years. Of the subjects, 88 (6.3%) admitted the use of cannabis once or more during their lives, including 80 men (11.4% of men) and 8 women (1.1% of women) ($P<0.001$, men vs. women). Seventeen (1.2%) were cannabis abusers, all of whom were men (2.4% of men). 17(2.4%) were men and none was a woman, $P<0.001$. Eighteen (1.3%) were cannabis dependent, including 13 men (1.9% of men) and 5 women (0.7% of women) ($P=0.058$, not significant). The most common reason reported for initial cannabis use was curiosity, and for current use was seeking pleasure. There were significant differences between occupations and cannabis use. Cannabis use was most common among the self-employed, second most common among government-employed and third most common among university students ($P<0.05$). There were also significant differences between level of education and cannabis use. Higher education was first, diploma holder was second, high school education was third and illiterate was the fourth most common cited educational level for cannabis users ($P< 0.05$).

Discussion

Cannabis use was found to be significantly higher in males than females. This is in contrast with studies conducted in the West showing that lifetime use did not vary significantly by sex.[8] In Iran, women usually suffer socially if they smoke or drink. Because this research was confined to Shiraz, a large city located in the South of Iran, care must be taken not to generalize these findings to the full Iranian population.

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BRIEF REPORT

NEEDLESTICK AND SHARPS INJURIES AT ASIR CENTRAL HOSPITAL, ABHA, SAUDI ARABIA

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McCormick and Maki were the first to highlight the risk of healthcare workers (HCWs) suffering harm from sharps injuries.[1] Since then, there has been an increase in awareness and concern about the acquisition of blood borne pathogens through needlestick injuries, especially with the advent of HIV.[2] The importance and seriousness of these infections were recently emphasized by the US Department of Labor.[3] The risk of such infections in health care workers has become a challenge because of high costs, labor incapacity, mortality and social stigmatization.[4] With the global increase in HIV and related infections, most health institutions have in place guidelines for prevention, reporting and management of needlestick and other sharp injuries, but the enforcement of such guidelines varies from place to place, as does the response by health care workers.

One of the commonest problems mitigating against proper management of sharps injuries has been the issue of non-reporting by health care workers. In a recent study of sharps injuries among Taiwanese health care workers, it was found that as many as 82% of sharps injuries were unreported.[5]

Several reports on sharp injuries among health care workers have emerged from the Kingdom of Saudi Arabia.[6-10] Like our report, these reports have highlighted the risky practices, the sources and locations of sharp injuries and the groups of staff most commonly affected. These reports have also highlighted some of the steps taken to reduce the incidence of sharps injuries among health care workers. However, to the best of our knowledge, our report is the first from Asir Central Hospital, a tertiary referral center in the Western region of Saudi Arabia. Our report also covers the longest period (ten years) of sharp injuries reported to date from the kingdom.

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Patients and Methods

Asir Central Hospital (ACH) (Abha, Saudi Arabia) is a tertiary health care center with over 500 beds. It trains nurses, technicians, undergraduate and postgraduate medical doctors, and has a work force of over 2000 personnel from over twenty different countries. It is the referral center for the Asir region of western Saudi Arabia. The hospital carries out qualitative health care services under the leadership of Western-trained consultants in almost all disciplines of medicine. It has an active infection control committee headed by an infectious diseases consultant.

The hospital has kept records of sharps injuries and their management since January 1991. However, until the year 2000, the program did not include mucous membrane and non-intact skin-blood exposures. An infection control nurse keeps meticulous records for every sharps injury case, and these data are computerized. The programme involves reporting every case of a sharp injury to the nurse-in-charge, who in conjunction with her colleagues and/or appropriate consultants in the hospital, carry out necessary follow-up tests, counseling and other management. Screening for baseline data on HBsAg, anti-HCV and anti-HIV antibodies is done for every affected staff and consenting source persons. At the time of employment every foreign doctor and nurse at ACH has had negative results since a negative result is a prerequisite for obtaining a residence permit. It is hospital policy that any health care worker found to be HBsAg negative post-exposure is further screened for anti-HBsAg; if negative, he/she is given HBV vaccine. The data covering ten years (1991-2000) were retrieved and analyzed. The c^2 and Fisher exact test were used for statistical analysis with significance set at P=0.05.

Results

There were few reported cases of sharps injuries in the first 5 years (1991-1995), possibly due to lack of awareness of reporting requirements among health care workers. However, between 1996 and 1999, the reporting situation had improved. The decline from the year 2000 is most likely due to the positive impact of health education by the infection control nurses. The areas of the hospital with the highest activities, such as the operating room (OR) and the adult and pediatric intensive care units (ICU), had the highest number of sharps injuries (Table 1). Table 2 shows the sources and incidence of sharps injuries in ACH. Needle recapping, careless disposal of sharps and blood extraction were responsible for over 50% of sharps injuries. These are easily preventable by health education.

Table 1. Sharps injuries by department and year at Asir Central Hospital.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total
Pediatric medical wards	-	-	-	-	-		1	1	1	1	4
Pediatric surgical wards	-	-	-	-	-		2	4	1	-	9
Pediatric intensive care units	-	2	-	2	-		3	3	1	1	13
Adult intensive care units	1	1	1	2	1		4	2	5	7	33
Female medical wards	-	-	1	1	1		2	3	1	-	13
Male medical wards	-	-	5	-	-		4	1	3	1	15
Female surgical wards	-	-	-	-	2		1	1	2	-	10
Male surgical wards	-	-	-	-	1		-	1	-	1	4
Emergency room	-	1	-	-	-		1	2	2	2	10
Operating room	-	1	-	-	1		1	2	4	2	15
Burns unit	-	-	2	-	-		1	1	-	-	3
Others	-	3	1	2	-		2	4	3	-	19
Total	1	8	10	7	6		22	24	23	15	148

Table 2. Sources and incidence of sharps injuries at Asir Central Hospital.

Sources of sharps injuries	Case no. (%)
Needle recapping	39 (26.4)
Garbage disposal	25 (16.9)
Blood extraction	17 (11.5)
During operation	14 (9.5)
IV insertion	11 (7.4)
Blade cuts	10 (6.8)
Uncovered needles	4 (2.7)
Needle on tray/trolley	4 (2.7)
Sorting of operating theatre linen	4 (2.7)
Skin test	3 (2.0)
Others	17 (11.5)
Total	148 (100)

Over 80% of sharps injuries in ACH occurred among nurses, cleaners and doctors (Table 3). Three quarters of the personnel involved were female nurses, with Filipinos and Indians constituting over 80% of cases. These figures represent the proportions of these health care workers in the employment of ACH and therefore are not statistically significant. However, the figures clearly show who should be targeted in prevention efforts.

Table 4 shows that 17/21 (81.0%) of those injured from source-positive cases showed up for follow-up compared with only 33/127 (26.0%) of those injured from source-unknown or source-negative cases. (P<0.05). Most of those injured from unknown sources (n=94) never returned for follow-up, possibly because they did not perceive themselves at risk of acquiring any of these infections. It is noteworthy that none of the source patients had HIV. However, two had HIV false positive ELISA results that were not confirmed by western blot. Also noteworthy is the fact that none of the twenty-one affected health care workers from the identified source positive cases (all of whom had negative baseline data) never seroconverted for the period of their follow-up. This number is rather small for any meaningful conclusions.

Discussion

Our data show a steady increase in the reported cases of sharps injuries in ACH, which reached a plateau between 1996 and 1999. Several factors might be responsible, including the sustained awareness efforts of the infection control department. That the figures had started to fall by the year 2000 indicates that a saturation point might have been reached both in the knowledge and reporting of sharps injuries by our health care workers. Needle recapping was the commonest cause of sharps injuries at ACH, and nurses were the most common victims. Garbage disposal and blood extraction were second and third as causes of sharps injuries whilst cleaners and doctors followed the nurses as the second and third largest victims.

These findings contrast with those of Huertas et al[4] where sharps injuries followed instrumental utilization followed by careless disposal of sharp devices. Recapping came fourth in their series and nurses were second after house keeping and maintenance staff, as victims. Our findings however agreed with those of Shanks and Al-kalai[6] and Memish et al,[10] in which nurses were the most affected employees. Also, global surveillance studies have shown that approximately two-thirds of all reported sharps injuries occur in nurses.[11] In the last two years, the use of puncture-resistant containers with disinfectant (Clorox) located at the most likely places for needlestick injuries to occur has drastically reduced the danger associated with needle recapping in ACH. It should however be noted that recapping of needles has been known as a no-

Table 3. Sharps injuries by personnel.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Total no. (%)
Nurses	-	2	9	5	3	20	13	13	10	11	86 (58.2)
Cleaners	-	4	-	-	2	4	4	6	4	2	26 (17.6)
Doctors	1	-	-	-	1	5	2	3	5	1	18 (12.2)
Clerks	-	-	1	-	-	-	2	1	1	-	5 (3.4)
Laundry staff	-	-	-	2	-	1	-	-	1	-	4 (2.7)
Ortho technicians	-	1	-	-	-	1	-	-	-	-	2 (1.4)
Respiratory therapists	-	-	-	-	-	1	-	-	-	1	2 (1.4)
CSSD technician	-	1	-	-	-	-	-	-	-	-	1 (0.7)
Student nurse	-	-	-	-	-	-	1	-	-	-	1 (0.7)
Incinerator staff	-	-	-	-	-	-	-	1	-	-	1 (0.7)
Porter	-	-	-	-	-	-	-	-	1	-	1 (0.7)
Driver	-	-	-	-	-	-	-	-	1	1	1 (0.7)
Total	1	8	10	7	6	32	22	24	23	15	148 (100)

Table 4. Follow-up profile of sharps-injured staff from source positive and negative patients.

	Follow-up profile					
Source confirmed diagnosis	Not followed-up	At 3 months	At 6 months	At 1 year	>1 year	Total
HCV positive	1	1	2	1	6	11
HBsAg positive	5	0	0	1	4	10
Total	6	1	2	2	10	21
Follow-up of staff with sharps injuries from unknown source and negative patients	29	2	1	1	0	33

benefit and high-risk procedure for more than two decades.[12]

Several suggestions have been made for preventing and limiting sharps injuries among health care workers.[11-13] These include health education, behavior change (e.g., not recapping needles, disposal-related issues), introduction of barriers to protect the caregiver, safer techniques, safer devices (e.g. needleless and self-sheathing equipment), and organizational factors such as improved staffing levels. However, the cheapest, easiest and most effective method of reducing sharps injuries is through health education, leading to changes in behavior. The preponderance of sharps injuries among our nurses may be related to the low nurse-to-patient ratio and the need to carry out many procedures in a hurry. This problem is not peculiar to our hospital and should be looked at critically by all who desire to effect changes.

Of the 21 sharps-injured staff from source-positive patients in our series, none seroconverted within the follow-up period. Huertas et al[4] found one HBV seroconversion out of ten surface antigen exposures, one in nine with an HCV-contaminated source, and none in 54 involving HIV contamination. Memish et al,[10] in their series, reported only one seroconversion to Hepatitis C.

Two of our HIV ELISA-positive source patients were not confirmed by western blotting, and thus were false positive cases. Although it took one week to get the western blot report on the two samples, no post-exposure prophylactic anti-retroviral drug was given to the affected staff because there was no clinical or epidemiological evidence of HIV disease in the source persons. This policy has however now changed to conform with the updated US Public Health Guidelines for the management of occupational exposures to HBV, HCV and HIV.[14]

This study has shown that education and preventive efforts should be directed at the nursing staff, cleaners and doctors. Future studies should address the issue of non-reporting of sharps injuries and the role of safer techniques, safer devices and organizational factors, such as staffing levels.

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FINE NEEDLE ASPIRATION IN THE MANAGEMENT OF THYROID NODULES: EXPERIENCE AT KING KHALID NATIONAL GUARD HOSPITAL, JEDDAH

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Nodular thyroid diseases are common, especially in mountainous areas of the western region of Saudi Arabia.[1] These nodules often present a diagnostic dilemma clinically as the distinction between benign and malignant lesions is not always obvious, making immediate planning of appropriate management difficult. Fortunately, the majority of these thyroid nodules are benign. Most are nodular goiter, which must be accurately distinguished from thyroid cancer. Thyroid cancer constitutes 5.4 % of all cancers in Saudi Arabia and is the second commonest cancer in females, with an age standardization rate of 3.5 per 100 000.[1]

Many techniques are available for use in the diagnosis of thyroid nodules, but they are expensive and associated with high morbidity rates. Fine needle aspiration (FNA) cytology is considered a minimally invasive, quick, cheap, effective and accurate primary mode of screening, diagnosing, and triaging patients with thyroid diseases.[2-4] Occasionally, this technique can be therapeutic, especially in cytic lesions.

In this report, we review our experience with this technique over a 4-year period at the King Khalid National Guard Hospital (KKNGH), Jeddah, to assess its usefulness and diagnostic accuracy in the management of thyroid nodules in our center.

Materials and Methods

The records of all FNA of thyroid nodules received in the Pathology Department at KKNGH, Jeddah, between January 1997 and December 2000 were retrieved and reviewed. The aspirations were carried out using either a 23G or 25G gauge needle attached to a 10 cc syringe with or without the use of the syringe holder. The aspirates were immediately smeared on standard microscope slides and either air-dried and stained with Diff-Quick stain or fixed in 95% alcohol and stained with Papanicolaou stain. The adequacy of each aspirate was assessed at the time of aspiration, on site and insufficient aspirates were immediately repeated. A maximum of 3 to 4 aspiration attempts were often performed on a patient during any clinic attendance to avoid haematoma formation. If repeated aspirates were still insufficient, the patient was given a 2 to 3 week appointment for a repeat FNA, or referred for ultrasound-guided aspiration, especially for nodules that are small, ill-defined or deep-seated.

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The cytological smears were reviewed microscopically and classified as either (1) benign (non-neoplastic), (2) follicular neoplasm, (3) indeterminate, (4) malignant or (5) inadequate. Indeterminate smears included cases in which hyperplastic nodules could not be differentiated from follicular neoplasm. Attempts were also made to classify the malignant lesions into follicular, papillary and medullary carcinoma or lymphoma.

Cases that had subsequent follow-up surgical resections were extracted from the record and their histological diagnoses were reviewed and correlated with their cytological diagnoses. The demographic data of all patients were extracted from the requisition forms and reports. The specificity, sensitivity and positive predictive value of the procedure were determined.

Results

A total of two hundred and fifty three cases of thyroid FNA were seen during the 4-year period and most were performed by the pathologists during the regular weekly FNA clinic. There were 225 females and 28 males and the ages ranged from 12 to 80 years with an average of 55 years. The peak age range of occurrence of thyroid nodules was 30 to 49 years, with this age group constituting 58.5 % of the cases.

Benign non-neoplastic lesions accounted for 56.5% (143 cases) with the majority, 51.8 % (131 cases) diagnosed as benign nodular goiter. Hashimoto's thyroiditis was present in 12 cases. Definite diagnosis of papillary carcinoma was made in 10.7 % of the cases. No case of lymphoma, medullary carcinoma or anaplastic carcinoma was detected in this series. Cases diagnosed as follicular neoplasms and indeterminate lesions constituted 51 (20.2%) and 15 (5.9%) of cases, respectively. Insufficient specimens accounted for 17 (6.7%) cases.

Table 1 shows the cytological and histological correlation of the 74 cases that had follow-up

Table 1. Cytohistological correlation of 74 cases with thyroid FNA + histology.

	Histology				
	Benign		Malignant		
Cytology	Goiter	Follicular adenoma	Follicular carcinoma	Papillary carcinoma	Total
Goiter	20	4	0	1	25
Follicular neoplasm	7	20	4	7	38
Indeterminate	1	0	0	0	1
Malignant	2	0	0	8	10
Total	30	24	4	16	74

thyroidectomy. The sensitivity and specificity was determined to be 89% and 92%, respectively.[*] There was good correlation amongst the benign cases with only one false negative case. The majority of cases reported cytologically as follicular neoplasms were follicular adenoma (24 cases) and only 4 cases were well-differentiated minimally invasive follicular carcinoma. Seven cases were subsequently diagnosed as follicular variant of papillary carcinoma. The only case classified as indeterminate on cytology was found to be multinodular goiter on histology. The two false positive cases were found to have benign goiter on histological analysis.

Discussion

King Khalid National Guard Hospital, a 500-bed tertiary center, serves Saudi Arabian National Guard members and their dependents, in addition to the general population through the Emergency Department of our private business center. A regular FNA clinic is run by the Anatomic Pathology Department where pathologists perform FNA on patients referred from other departments.

FNA has been extensively documented as a useful and reliable technique in the assessment of thyroid nodules, with specificity and sensitivity rates varying from 75 to 100 % in various reports.[2-4] The specificity of 92% and the sensitivity of 89% achieved in our study correlates with reports of other studies establishing that FNA of thyroid is a safe, reliable and effective method for differentiating benign from malignant nodular thyroid lesions in our center. The performance and organization of the FNA clinic by pathologists and strict specimen adequacy rules have proved to be useful and likely responsible for the high sensitivity and specificity achieved. In our clinic, specimen adequacy is assessed immediately and FNA is repeated at a single attendance whenever an insufficient specimen is detected. This approach ascertains adequate sampling and superb technical quality while limiting the number of unsatisfactory aspirates.

In various reports, up to 10 % of FNAs are considered indeterminate and these are usually due to overlapping cytological features between adenomatous hyperplastic nodules and follicular neoplasms.[5-7] In our series, only 15 cases (5.9%) were classified as indeterminate. Another major limitation encountered is differentiating follicular adenoma from minimally invasive well-differentiated follicular carcinoma. Although many studies have tried to correlate cytological features, such as cell size, and nuclear overlapping, and clinical features such as nodule size, age > 40 years and male sex, none of these has been found to be consistently reliable.[7] This difficulty in reliable differentiation of follicular adenoma from low-grade follicular carcinoma by FNA is highlighted in this series; 4 cases classified as follicular neoplasm were subsequently diagnosed as low-grade follicular carcinoma. Fortunately, the management of these lesions does not differ significantly. Of note, however, is that 24 of the 35 cases (68.5%) cytologically categorized as follicular neoplasm were accurately diagnosed as true follicular neoplasm (20 adenoma and 4 carcinoma). Careful evaluations of cases with features of follicular lesion have been instituted to limit this, but these problems still remain difficult. The two false positive cases turned out to be nodular goiter, which highlights the difficulty in distinguishing between the papillary hyperplastic foci of nodular goiter and carcinoma. Using strict cytological nuclear criteria of papillary carcinoma can help to eliminate this problem.

In conclusion, our study confirms other reports that FNA of thyroid is a safe, reliable and effective method for differentiating benign from malignant thyroid nodules. The skillful application of FNA technique with recovery of adequate sample by on site evaluation of the cytological preparation will decrease interpretative errors and significantly improve the diagnostic accuracy of thyroid FNA. Surgeons also use the information provided on FNA in triaging and counseling patients prior to surgical intervention and planning subsequent management.

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[*] % sensitivity = 8/8+1 x 100 = 89%; 25/25+2 x 100 = 98%. The true negative includes 24 goiters and 1 case diagnosed as indeterminate; follicular adenoma was considered negative.

EXCISION BIOPSY OF PERIPHERAL LYMPHADENOPATHY IN CHILDREN IN A COMMUNITY HOSPITAL

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Lymphadenopathy in the pediatric age group is a common manifestation of a large variety of disorders, both benign and malignant, but it is often difficult clinically to determine the cause and identify which patients will benefit from lymph node biopsy.[1-3] Added to this are regional and geographic etiological variations in pediatric lymphadenopathy.[4,5] This study is an etiologic evaluation of 71 children with peripheral lymphadenopathy that includes an analysis of the cause in relation to age of the patients, sex, and site and size of the lymph nodes.

Patients and Methods

The medical records of all children aged 12 years or less who had a peripheral lymph node biopsy as part of their diagnostic evaluation at our hospital between January 1989 and December 2001 were reviewed retrospectively for age at diagnosis, sex, site of lymphadenopathy, and diagnostic evaluation. In all patients, a lymph node biopsy was performed when a significantly enlarged lymph node persisted or increased in size and other diagnostic tests failed to show etiology or when the lymph node was thought to be abnormal by the treating physician given the site and age of the child. A large number of these children received antibiotics by their treating physician prior to their referral for lymph node biopsy.

All lymph node biopsies were performed under general anesthesia, and the slides were reviewed by one pathologist. The size of lymph node as well as the histological diagnosis was obtained from the histopathology report. The etiology of lymphadenopathy was broadly classified as specific when a cause was shown as either benign or malignant and non-specific or reactive when no definite cause could be found.

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Results

Seventy- one children, including 47 males and 24 females (M:F of 1.96:1), had peripheral lymph node biopsy as part of their diagnostic evaluation at our hospital. Their distribution according to age and sex is shown in Table 1. The majority were 5- to <10-years of age (40.8%). Of 71 children, 34 (47.9%) had a specific diagnosis and in the remainder, the lymph nodes were reactive. Only nine children (12.7%) were less than 1 year of age, but 4 (44.4%) of those had a specific diagnosis. Nineteen were in the 10- to 12-year age group, and 52.6% had a specific diagnosis. Fourteen children were in the 1- to <5 -year age group, but only 14.3% had a specific diagnosis.

Of 71 children, 34 (47.9%) had a specific diagnosis, including 23 males and 11 females (M:F of 2:1). The distribution of lymph nodes according to site and number with specific diagnosis is shown in Table 2. The majority of our patients (71.8%) had biopsy of cervical lymph nodes, while only one child had biopsy of the supraclavicular lymph node. This was a 10-year-old male child diagnosed with Hodgkin's disease of mixed cellularity. Eight of our patients had axillary lymphadenopathy, but only 3 of those were positive for a specific diagnosis, which was granulomatous in all, secondary to tuberculosis in one and reactive to BCG in the other two. Four of our six patients with inguinal lymphadenopathy had a specific diagnosis of non-Hodgkin's lymphoma, Hodgkin's disease of mixed cellualrity, histocytosis X, and dermatopathic lymphadenopathy (one each). Three of five with submandibular lymphadenopathy were positive for the specific diagnoses of tuberculosis, Castleman`s disease, and metastasis from an astrocytoma (one each).

The causes for lymphadenopathy according to age and sex are shown in Table 3. Of those with a specific diagnosis, 22 (64.7%) had lymphoma (20 Hodgkin's disese and 2 non-Hodgkin's lymphoma). Fourteen were males and 8 were females, and 15 (68.2%) were in the 5- to <10-year age group, while the other 7 (31.8%) were in the 10- to 12-year age group. The distribution of the different histologic types of Hodgkin's disease were as follows: 9 with nodular sclerosis, 7 with mixed cellularity and 4 with lymphocytic predominance. The sizes of lymph nodes were obtained from histopathology reports, which had precise measurements. The pathology measurements did not however reflect the actual size of the biopsied nodes as some of them were probably incomplete

Table 1. Distribution of lymph nodes according to age and sex.

	0 to <1 year	1 to <5 years	5 to <10 years	10 to12 years	Total
Males	7	7	21	12	47
Females	2	7	8	7	24
Total	9	14	29	19	71

Table 2. Distribution of lymph nodes according to site and no. with specific diagnosis.

Site of Lymph Node	Total No.	%	No. with specific diagnosis	%
Cervical	51	71.8	23	45
Axillary	8	11.3	3	37.5
Inguinal	6	8.5	4	66.7
Submandibular	5	7	3	60
Supraclavicular	1	1.4	1	100
Total	71		34	47.9

excisions. The size of lymph nodes in those with specific diagnoses ranged from 0.8 to 5 cm (mean, 2.5 cm), while the size in those with non-specific diagnoses ranged from 0.5 to 4 cm (mean, 1.6 cm). None of our patients who had reactive hyperplasia (52.1%) was subsequently proved to have a specific diagnosis.

Discussion

Peripheral lymphadenopathy, which poses a diagnostic challenge for physician, is a relatively common condition in the pediatric age group. Most patients can, however, be diagnosed on the basis of a careful history, physical examination and relevant laboratory tests. Although the majority of children have benign lymphadenopathy of unknown etiology, a small group will have serious life-threatening benign and malignant diseases. It is in this group of children that it is sometimes difficult to define who will require and benefit from a lymph node biopsy to confirm the diagnosis.[1-3] To avoid delay in diagnosing serious diseases, one approach is simply to excise all enlarged peripheral lymph nodes, but this will lead to unnecessary biopsies. As a result, a selective policy of biopsying only those children with a high probability of having serious disease was advocated. Several studies have attempted to define the group of children who would benefit from a lymph node biopsy based on the age of the child, site, size and number of lymph nodes involved, duration of symptoms, clinical features, and relevant laboratory tests, but so far there are no well established criteria.[1-3,5]

In our study, age was not particularly helpful in suggesting the possibilty of a serious disease. The chance that lymphadenopathy is due to a specific diagnosis was relatively the same among the different age groups. The only exception was the 1- to <5-year age group, where only 14.3% had a specific diagnosis. The relative lack of a specific diagnosis in this age group is not suprising since a large number of children at this age have recurrent upper respiratory tract infections with associated reactive cervical lymphadenopathy. In this group, and in the absence of other suggestive features, serial observations for spontaneous resolution seem to be the most reasonable course. However, like others, we advocate biopsy of the lymph node if there is an increase in size at follow up or if the lymph node persists after 4 to 6 weeks of follow-up.[1] Some authors also advocate a course of antibiotics.[6] A large number of our patients received antibiotics prior to their referral for biopsy. The value of antibiotics in reactive hyperplasia needs to be clarified. On the other hand, the clinical differentiation of bacterial lymphadenitis from other causes of lymphadenopathy is usually not difficult. These children should be treated with a course of antibiotics, which usually produces resolution of symptoms and decreases the size of lymph nodes, or the infection localizes, necessitating incision and drainage.

Our overall male:female ratio was 1.96:1, but like others we found a male predominance in patients less than 12 years of age with lymphoma.[1,7] None of our patients had generalized lymphadenopathy, which is usually not common in the pediatric age group, but is known to have a specific diagnosis in the majority of cases.[5] Lymph nodes in the cervical region drain areas that are common portals of entry for a large variety of infectious agents. This makes them the most commonly involved nodes, and as expected reactive hyperplasia occurred most frequently in the cervical lymph nodes. Like others, our study confirms the fact that the vast majority of peripheral lymphadenopathy in children is of unknown origin, but no site was totally free from serious diseases. Only one of our patients had biopsy of the supraclavicular lymph node, which may reflect the rarity of involvement of this group of lymph nodes in children. Involvement of this group of lymph nodes may be rare, but the chance of malignant involvement is high.[1,3,5] This possibility calls for early biopsy of enlarged supraclavicular lymph nodes in children.

In our respective study, the population was partially selected because some were referral cases from the pediatric oncology unit at our hospital. This factor is clearly reflected by the high frequency of malignant

Table 3. Distribution of causes of lymphadenopathy according to age.

Diagnosis	0 to <1 year	1 to <5 years	5 to <10 years	10 to 12 years	Total
Reactive	5	12	12	8	37
Granulomatous	2	0	1	2	5
HistocytosisX, Castelman's disease, Chronic inflammation	2	2	0	1	5
Hodgkin's disease	0	0	13	7	20
Non-Hogkin's lymphoma	0	0	2	0	2
Metastatic	0	0	1	1	2
Total	9	14	29	19	71

lymphadenopathy in our series. There were 24 malignant lymphadenopathies among the 71 (33.8%) children with lymphadenopathy, including 34 (70.6%) with a specific diagnosis. The majority (58.8%) had Hodgkin`s disease. Karadeniz et al reported 56.7% malignant lymphadenopathy among 104 children with a specific diagnosis, and 29.8% of them had Hodgkin`s disease.[5] The importance of regional variation in the causes of lymphadenopathy also needs to be emphasized. Normal lymph nodes vary in size and there are no known criteria based on size for differentiating normal from abnormal lymph nodes. Barness gave the most specific and useful criteria available: nodes less than 3 mm in diameter are normal, cervical and inguinal nodes up to 1 cm in diameter are normal up to the age of 12 years, and palpable lymph nodes in newborns are abnormal.[8] Lymph node size is an important factor in evaluating children with peripheral lymphadenopathy. A maximum diameter >2 cm was reported as the appropriate limit to distinguish malignant or granulomatous disease from the others.[2,5] In our study, like others, the causes of lymphadenopathy were more frequently benign in patients with maximum lymph node diameters < 2 cm. Only 3 (8%) of 37 with reactive hyperplasia had lymph nodes with a maximum diameter > 2 cm, while all but 8 of those with a specific diagnosis had lymph nodes with a maximum diameter >2 cm. Thus, a lymph node size of 2 cm can be considered an appropriate limit to distinguish those with specific diagnosis from those with reactive hyperplasia. However, this is not the case for those with supraclavicular lymph nodes where the majority, based on published literature, have a specific etiology, even if > 2 cm in diameter.[1,3,5]

In conclusion, lymphadenopathy is a relatively common condition in the pediatric age group, and although a large number will be reactive hyperplasia of unknown etiology, about 50% to 60% of those who undergo lymphnode biopsy will have a specific diagnosis. Unfortunately, there are no clear criteria outlining which patients will benefit from a lymph node biopsy and clinical judgement remains the most important factor in this regard. Neither the site of the lymph node, nor the age of the child were predictive variables, but children in the 1- to <5 -year age group were more likely to have benign reactive hyperplasia. In the absence of other relevant factors, this group of children should be observed. Biopsy should be done if there is an increase in the size of the lymph node or if the lymph node persists after 4 to 6 weeks of follow-up. Children with lymph nodes >2 cm in diameter and those with supraclavicular lymphadenoapthy should undergo biopsy early.

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SERUM MALONDIALDEHYDE LEVELS IN *TOXOPLASMA* SEROPOSITIVE PATIENTS

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Toxoplasma gondii (T. gondii) has very low host specificity, and will probably infect almost any mammal. Like most of the Apicomplexa, *T. gondii* is an obligate intracellular parasite. Its life cycle includes two phases called the intestinal (or enteroepithelial) and extraintestinal phases. The intestinal phase occurs in cats only and produces "oocysts." The extraintestinal phase occurs in all infected animals and produces "tachyzoites" and, eventually, "bradyzoites" or "zoitocysts." The disease toxoplasmosis can be transmitted by ingestion of oocysts or bradyzoites.[1-3]

In most humans infected with *T. gondii*, the disease is asymptomatic. However, under some conditions, toxoplasmosis can cause serious pathology, including hepatitis, pneumonia, blindness, and severe neurological disorders. This is especially true in individuals whose immune systems are compromised (e.g., AIDS patients).[1-4] In humans, toxoplasmosis can be transmitted transplacentally if a woman is infected with toxoplasmosis while she is pregnant. Thus, women are often told to minimize contact with cats while they are pregnant, and to avoid emptying their cat's litter box.[1-3] However, pregnant women must also remember that oocysts are not the only source of infection, and take additional precautions to prevent infections via raw or undercooked meat.[3,5]

The central nervous system is especially vulnerable to free radical damage due to the brain's high oxygen consumption rate, its abundant lipid content, and the relative paucity of antioxidant enzymes compared with other tissues. In an immunocompromised host, toxoplasmosis can be a very serious disease, and can occur if a person is infected with toxoplasmosis before or after his/her immune system is compromised. In particular, toxoplasmosis can cause severe neurological disorders and pneumonia in patients with human immunodeficiency virus (HIV). In HIV-infected patients, infection with *Toxoplasma* usually develops as a brain infection.[3,6,7]

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Lipid peroxidation is a well-established mechanism of cellular injury in humans, and is used as an indicator of oxidative stress in cells and tissues. Lipid peroxides, derived from polyunsaturated fatty acids, are unstable and decompose to form a complex series of compounds. These include reactive carbonyl compounds, of which malondialdehyde (MDA) is the most abundant. Therefore, measurement of malondialdehyde is widely used as an indicator of lipid peroxidation. Increased levels of lipid peroxidation products have been associated with a variety of chronic diseases in both humans and model systems.[8-10] For example, HIV infection is associated with oxidative stress, as has been demonstrated in adult, seropositive individuals. One study showed that serum malondialdehyde (MDA) concentration in HIV-infected children was significantly higher than in control children.[6,7] The aim of this study was to investigate the difference in the serum malondialdehyde levels (an end-product of lipid peroxidation) between normal and *T. gondii*-infected individuals (IgG seropositive but no symptoms).

Methods

We assayed MDA activity in the serum of 100 subjects aged between 18 to 70 years (50 males and 50 females). None were smokers, or had any known pathologies (progressive neurodegenerative disease, atherosclerosis, psoriasis, etc) and none were taking steroids or medications such as iron for anemia at the time of sampling. Fifty patients and 50 controls were examined in this study. The mean age of the patient group, which consisted of 25 men (aged 41±17 years) and 25 women (aged 38±13 years). The mean age of the control group, which included 25 men (aged 40±14 years) and 25 women (aged 37±13 years). Serum samples for the control group were obtained from healthy people who had come to the different departments of Erciyes University/Medical Faculty for a regular check-up and from students or employees of the University. All subjects fasted after midnight before blood collection the next morning.

The micro ELISA technique for *T. gondii* was used to assess seropositivity. Anti-*T. gondii* IgG and IgM antibody ELISA kits were purchased from EUROIMMUN. The technique followed the manufacturer's instructions. The 50 patients were IgG seropositive and the 50 healthy control subjects were seronegative. All subjects were IgM seronegative.

All venous blood samples taken between 8 and 9 a.m. after 12 hours of fasting were collected in polystyrene tubes and vacutainers containing heparin. The tubes were centrifuged at 500xg for 15 min. Serum was then removed and stored at -20ºC until analysis. Serum MDA levels were measured by the double heating method.[11,12] The principle of the method is based on the spectrophotometric measurement of the color that occurs during the reaction to thiobarbituric acid with MDA. The concentration of thiobarbituric acid reactive substances (TBARS) was calculated by the absorbance coefficient of malondialdehyde-thiobarbituric acid complex and expressed in nmoL/mL.

Statistical analysis was performed with SPSS software package (Version 11.0 for Windows). Data were expressed as mean±standard deviation (SD). For comparison of the two groups, the non-parametric Mann Whitney U test was used. A probability value of $P<0.05$ indicated a statistically significant difference.

Results

The difference in MDA levels between patients and controls was statistically significant both for females ($Z=5.99$, $P<0.05$) and males ($Z=6.06$, $P<0.05$) (Table 1). No correlation was found between age and MDA levels ($P>0.05$) in either female or male patients or controls.

Discussion

This is the first study to characterize the relationship between *T. gondii*, (which can cause serious pathology, including hepatitis, pneumonia, blindness, and severe neurological disorders) and MDA (lipid peroxidation), which is a well-established mechanism of cellular injury in human, and used as an indicator of oxidative stress in cells and tissues.

Gross lesions by *T. gondii* involving the nervous system are limited and include occasional submeningeal hyperemia and hemorrhage, hemorrhagic infarction, cerebral edema that can be sufficiently severe to cause displacement and herniation, and ventricular dilatation. In addition, early microscopic lesions are characterized by degeneration of vessels walls and edema. Following ingestion, bradyzoites from tissue cysts or sporozoites from oocysts are known to penetrate the intestinal epithelial cells and multiply in the intestine. There is also strong evidence that *T. gondii* invades host cells by active penetration and not by phagocytosis. Organisms may then spread locally to mesenteric lymph nodes, Peyer's patches, and other cells, where they multiply as tachyzoites by repeated intracellular endodyogeny during the acute phase of the infection. With chronicity, tachyzoites of *T. gondii* transform into slowly growing bradyzoites that replicate within tissue cysts.[13] In the immunocompromised or immunodeficient patient, a cyst rupture or primary exposure to the organisms often leads to lesions. The organisms can be disseminated via the lymphatics and the bloodstream to other tissues. Animal studies suggest that disintegration of cysts may give rise to clinical encephalitis in the presence of apparently adequate immunity.[14]

Immune-mediated mechanisms have been proposed as explanations for vascular injury (type III hypersensitivity) and cellular necrosis (type IV hypersensitivity). Immune cytotoxic T-lymphocytes (CD8+ T cells), which play a defensive role because of their ability to lyse infected cells, could also potentially be involved in causing tissue damage. Intracellular growth of tachyzoites has also been advanced as a cause of necrosis.[13]

Levels of MDA were significantly increased in *Toxoplasma* seropositive patients (IgG seropositive but no symptoms). The results of our study strongly suggest that one of the main reasons for high MDA levels in *Toxoplasma* seropositive patients could be decreased activity of the defense system protecting tissues from free radical damage. However, in patients and controls, no correlation was found between age and MDA levels in either females or males. In addition, no significant correlation could be found between MDA levels of either females and males for *T.gondii*-infected and control groups. These results for *Toxoplasma* seropositive patients could possibly be explained as indicating high MDA activity in all ages.

Lipid peroxidation is a free radical-related process that may occur under enzymatic control (e.g., for the generation of lipid-derived inflammatory mediators) or nonenzymatically in biologic systems. This latter form is associated mostly with cellular damage as a result of oxidative stress, which also involves cellular

Table 1. Malondialdehyde (MDA) concentrations of *Toxoplasma* seropositive patients and seronegative controls.

	Patients	
	Age (years)	MDA (nmoL/mL)
Female (n=25)	38 ± 13	0.95 ± 0.22
Male (n=25)	41 ± 17	0.91 ± 0.18
	Controls	
Female (n=25)	37 ± 13	0.26 ± 0.18
Male (n=25)	40 ± 14	0.20 ± 0.10

Values are mean±SD

antioxidants.[10] The high infection/control ratio of MDA concentration and the significant correlation strongly indicate the occurrence of oxidative stress and lipid peroxidation as a mechanism of tissue damage in cases of chronic toxoplasmosis.

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MORTALITY DATA FOR CYSTIC FIBROSIS PATIENTS IN A TERTIARY CARE CENTER IN SAUDI ARABIA

Table 1. Weight-for-height Z scores during 2 years of follow-up in cystic fibrosis patients.

Time (months from diganosis)	Weight-to-height Z score (means)	No. of patients	Statistical comparison (*P* value vs previous follow-up visit)
Diagnosis	-1.7±0.16	74	–
6	-0.77±2.0	74	0.0001
12	-0.86±1.01	58	0.918
18	-0.89±1.01	48	0.588
24	-0.98±1.01	46	0.703

To the Editor: The incidence of cystic fibrosis (CF) in Saudi Arabia was reported as 1 in 4243 children.[1] Epidemiological and genetic data have been reported in detail for many Gulf countries,[2-5] but not mortality data for Arabian countries. In this report we describe factors that contribute to mortality in the largest CF population in the Gulf area.

The charts of all CF patients referred to our center during the period from November 1994 to October 1998 were reviewed. Our center is considered the only referral center for all CF patients in Saudi Arabia. Cystic fibrosis was diagnosed by the typical clinical picture and a high sweat chloride in two consecutive tests (>60 mmol/L by the quantitative method) (Wescor, USA). We determined weight and height for age and weight-for-height Z scores. The calculated weight is the actual weight expressed as the percentage of ideal body weight and calculated height is expressed as a percentage of actual height divided by the 50th percentile height for age.[6] A Z score was defined as the standard deviation of weight and or height from the mean of a reference population.[7] All confirmed CF patients had their weight and height measured at the first visit and at each follow up visit thereafter, usually every 2 to 4 months.

A respiratory culture, which includes sputum or a nasopharyngeal aspirate in smaller children, is taken routinely on initial diagnosis and at every clinic visit thereafter. All patients with respiratory symptoms that included tachypnea, increased sputum production and wheezing are started on prophylactic broad-spectrum antibiotics for the first 1 to 2 years as recommended.[8-10] Such antibiotics include one of the following: amoxicillin, cephalexin monohydrate, or trimethoprim/sulfamethoxazole (Bactrim).[6-10] Anti-microbial prophylaxis is then re-evaluated according to persistence of bacteria and given only during acute attacks. Patients who do not respond to both oral antibiotics and inhaled gentamicin during acute attacks [8,11,12] are admitted for therapy with intravenous antibiotics, including a third-generation cephalosporin and an aminoglycoside, according to culture results. [8,11,12] All patients with signs and symptoms of pancreatic insufficiency such as diarrhea or positive fat in the stool are started on pancreatic enzymes, according to Cystic Fibrosis Foundation recommendations, [6] and fat-soluble vitamins (A, D, E and K).

One hundred and eighty three CF patients were diagnosed during the period from November 1985 to September 2003. One hundred and forty nine (81%) CF patients are alive, 34 (19%) died. Ninety-three (51%) were males and 90 (49%) were females. Age at diagnosis was 3±3.8 years (mean). The mean follow-up period was 4.3±3.3 years with a range of 0.01 to 18 years. Mean weight at diagnosis was 9.5±7 kilograms, with a range of 2.4 to 36 kilograms. Calculated weight/height was 82±19%, with a range of 40±162%. Sixty-five percent of patients were in the mild to moderate malnutrition stage (<90th percentile), and 35% in the normal level for their weight/height. Calculated height/age was a mean of 91±12 centimeters, with 63% having mild to moderate stunted growth. The weight/height score showed improvement in the first six months from −1.7±0.16 to −0.77±2 (P=0.0001), but reached a plateau thereafter at 12, 18 and 24 months (P>0.05)(Table 1). The height/age Z score showed no significant improvement in the first 12 months, but there was an improved response at 18 and 24 months (data not shown).

Factors that were significantly related to progressive lung disease and early mortality of CF patients were calculated weight/height (P=0.01) and albumin level at follow up (P=0.001), high HCT (P=0.0002), low MCHC (P=0.01), low MCV (P=0.0002), date of development of *Pseudomonas* resistance to gentamicin (P=0.04), date of resistance to ampicillin (P=0.07), positive (+ve) culture of *Pseudomonas* (P=0.01), +ve MRSA (methicillin-resistant *Staphylococcus aureus*) (P=0.02), and development of resistance to the following antibiotics: gentamicin (P<0.0001), amikacin (P=0.0002), ceftazidime (P≤0.0001), ciprofloxacin (P≤0.0001), piperacillin (P=0.0005) and imipenem (P=0.01).

Our study has shown that early mortality from CF is multifactorial, but mainly due to factors related to early diagnosis and proper management, with emphasis on early nutritional rehabilitation. Our analysis also showed that early development of multi-resistant *Pseudomonas* has a significant relationship to mortality. One hypothesis that explains the development of multi-resistant bacteria is the use of long-term continuous gentamicin nebulization treatment to prevent frequent hospitalization. Intermittent gentamicin nebulization treatment instead of a continuous regimen may need to be adopted.[11] MRSA colonization has been reported in CF patients,[13] but its contribution to mortality has not been recognized. Our study has shown a significant relationship to mortality (P=0.02). The initial presentation in most of our patients was normal hemoglobin with a hypochromic-normocytic picture. Further follow up of these patients found a poor prognosis in patients who developed a high hematocrit, low MCV, low MCHC and low albumin due to increased erythropoietin activity in the presence of normal hemoglobin. This gives a false high hemoglobin level in the presence of anemia due to chronic infection and malnutrition. To our knowledge, this is the first study that shows the relationship of hematological indices to mortality in the Gulf area.[13,14] Other factors that may have contributed to mortality but were not included in our study are the role of advanced lung disease, the different types of CFTR (cystic fibrosis transmembrane receptor) mutations, and poor compliance to treatment and adherence to chest physiotherapy. Further studies are needed to evaluate whether these factors are related to mortality.

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A SURVEY ASSESSING PATIENT SATISFACTION AT PUBLIC AND PRIVATE HEALTHCARE FACILITIES IN RIYADH, SAUDI ARABIA

To the Editor: Quality is a process of meeting the needs and expectations of the customers. Although quality has many perspectives, each customer has specific needs and expectations and the goal is for these expectations to be fulfilled by the provider organization. One method for the identification of customer needs and expectations is a satisfaction survey. Any system has three components: inputs, processes and outputs. Outputs and outcomes are the results of the processes and the activities of the system. One measure of this component is the rate of satisfaction of the users of the system. In healthcare, the ultimate user of the system is the patient and thus, the patient survey is the method most appropriate to measure satisfaction with outputs and outcomes of the system.

The field of patient satisfaction surveying is growing. With most of the accrediting bodies such as JACHO, NCQA, AAAHC and URAC requiring survey results to be reported on a regular basis, mechanisms for addressing them must be implemented and measured. This emphasis on patient satisfaction has created a new type of health care customer, one who is becoming increasingly intolerant of mediocre care and service.

Several studies of patient satisfaction in both primary health care and inpatient settings have shown that patient satisfaction is directly correlated to patient's expectation, but not necessarily to clinical outcomes. [1-5] Two studies are worthy of note relating to Saudi Arabia (El-Shabrawy and Mahmoud, 1993[6] and Mansour and Al-Osimy, 1993[7]). Both report on surveys conducted in Riyadh, Saudi Arabia with patients in primary health care (PHC) settings. Using interview methodology, both studies collected information from a randomly selected sample of patients regarding satisfaction with care and services received at the PHC centers. Both studies reported patients to be satisfied with their care in general, but they were less pleased with the waiting times and the thoroughness of their visits.

This letter describes a study performed to assess patient satisfaction in Riyadh, Saudi Arabia. Our analysis focused on assessing the relationships between patient characteristics and level of satisfaction and previous history with the facility from which they sought care. Patients were selected from public and private primary health care and inpatient care sectors. The objectives were to measure satisfaction by each variable identified in terms of service and care. We also sought to measure the difference in satisfaction between these groups and find out if there were any correlations with the type of the facility and the satisfaction level of the patient.

The target population was patients attending two MOH and five private hospitals (the number of private hospitals was increased because they have fewer inpatients) and five MOH PHC centers in Riyadh, Saudi Arabia. A sample of patients representative of those attending the facilities were selected using stratified random sampling techniques. Only inpatients with at least a 3-day stay were included. A structured questionnaire was developed and 500 copies were distributed to hospitals and 500 to PHC centers. Of the 500 hospital questionnaires sent out, 392 (78.4%) were returned and used in the analysis. From the PHC centers 408 questionnaires (81.6%) were returned and validated.

The study instrument consisted of questions on demographic information with one satisfaction question asking whether the patient would likely return to the facility a second time. Satisfaction was also assessed by the four-point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree). The satisfaction measures assessed patients' views about a variety of important hospital and PHC characteristics, including the availability of services, accessibility of the facilities to patients, the quality of the accommodation, affordability, the quality of facility personnel, including doctors, nurses and other staff, and the cleanliness and appearance of the facilities.

The questionnaire had face validity based on health professional and patient comments, and was determined to be reliable, having an 88.2% coefficient alpha from pilot testing on 10 inpatients and 10 outpatients. We used logistic regression analysis to assess the volume and direction of the relationships between the independent and dependent (dichotomous variable) variables.

The source of payment for patients' care, and patients' level of education were the factors that most significantly impacted on satisfaction with the various aspects of care investigated in the study. These factors were independent of provider type (hospital or clinic), ownership (public or private), source of payment, and patient level of education. Patients attending primary care clinics were more likely than those attending hospitals to be satisfied with the availability of providers and services and their ease of access to the facility. In particular, clinic patients were significantly satisfied with the availability of specialists (odds ratio, 3.82; 95% CI, 2.22-6.57), felt the facility was sufficiently high tech (4.00; 2.30-6.93), appreciated the presence of Saudi doctors (1.96; 1.18-3.25), were satisfied with the quality of the non-physician and nurse staff (3.03; 1.71-5.39), had family living near by (1.75; 1.02-3.01), and had attended the facility because they had heard good things about it from others (12.62; 1.56-4.38) or a family member had a previous positive experience with the facility (1.66; 0.98-2.81). Specifically they did not think their facility was located sufficiently close to their residence (0.42; 0.25-0.70), were dissatisfied with the scheduling of appointments (0.50; 0.30-0.84), felt costs were too high (0.50; 029-0.87), and were not happy with the religious make-up of the staff (0.36; 0.21-0.60). Patients who attended private institutions were also dissatisfied with most of the factors in the survey. Items they were not significantly dissatisfied with included the availability of providers of the same sex, the ease to get to the facility, the length of waiting time, the ease of registration and scheduling of appointments, and the presence of Saudi doctors.

For the most part, individuals who paid for care from personal resources or those of the family (private pay) were most dissatisfied with the facilities they attended. Private-pay patients were significantly dissatisfied with the availability of specialists (0.56; 0.34-0.94), the ease of registering (0.58; 0.36-0.94), the quality of doctors available (0.64; 0.38-1.06), the quality of manners (0.54; 0.33-0.89), and the religion of facility staff (0.64; 0.39-1.05). They were satisfied with their ability to move around in their facility (0.64; 0.39-1.65), and the presence of Saudi doctors (1.53; 0.94-2.49).

The relationship between education level, and facets of patient satisfaction were consistently and significantly positive in direction. Patients with more years of education tended to be more satisfied with factors such as the availability of entertainment at their facility (2.24; 1.44-3.50), the facility's proximity to their residence (1.71; 1.10-2.68), shorter waiting times (1.48; 0.94-2.33), cost of care (2.05; 1.24-3.40), quality of the doctors (1.57; 0.97-2.53), the cleanliness of the facility (1.72; 1.09-2.72), and the nationality (1.50; 0.93-2.40) and religion of the staff (1.48; 0.94-2.34). Patient age made a significant difference in reported satisfaction for only two items. Older patients tended to be more satisfied with the availability of entertainment in the facility they attended (1.02; 1.00-1.04), and the religion of the staff (1.02; 1.00-1.04). Living situation did not seem to make a difference with respect to patient satisfaction. Patients who were married as well as those who lived alone tended to be dissatisfied with the facilities they attended. Both married patients and those living alone tended to be dissatisfied with the availability of providers of the same sex, and the proximity of the facility to their residence. Patient family size was significantly related to only one satisfaction item. Patients coming from large families tended to be more satisfied with the appropriateness of appointments to the facility they attended (1.12; 1.04-1.20).

The employment status of patients made a significant difference in reported satisfaction in six areas. Employed patients were more satisfied with how close their facility was to family living near by (2.02; 1.13-3.61), the technological sophistication of the facility (1.62; 0.92-2.85), the presence of Saudi doctors (3.16; 1.81-5.50), the quality of the nursing staff (2.27; 1.27-4.05), and felt the cost of care was appropriate (1.73; 0.96-3.10). They were, however, not satisfied with the religion of the staff at the facilities they visited (0.50; 0.29-0.88).

The income level of patients as reflected by reported salary were significantly related to three items and all in a positive direction. Patients with higher salaries were more likely to be satisfied with the quality of the nursing staff (2.02; 1.27-3.21), and had a previous positive experience as a patient (1.56; 0.97-2.50) or knew of family member who had a previous positive experience at the facility they attended (1.94; 1.22-3.08). In contrast to the responses of patients with higher salaries, those who reported having a second source of income were more likely to be negative about their experiences. Patients with second incomes were significantly dissatisfied with the amount of time they had to wait for service (0.60; 0.33-1.10), the ease with registering (0.56; 0.31-1.00), and felt the cost of care was not appropriate (0.53; 0.28-1.03).

Patient health status was not significantly related to satisfaction with specific aspects of the facilities they attended. However, patients who had poor self-reported health status were significantly related to two 'prior history' factors i.e., more likely to have had a family relationship with a staff member (2.04; 1.23-3.40), and they felt the hospital had a good reputation (2.09; 1.27-3.46). On the other hand, patients with good self-reported health were significantly less satisfied with the nationality of the staff at the facility they attended (0.64; 0.39-1.07).

Of all the patient characteristics only sex did not significantly affect patient responses on any of the items on the satisfaction scale.

The most crucial challenge for all those who work in healthcare organizations, including those who manage them, is to ensure an exclusive standard of quality for their customers, particularly the patients. The importance of having continuous quality improvement principles must be embedded in the framework of an organization, in order to attain customer or patient satisfaction.

Healthcare organizations should focus on the importance of the care process from the patient's viewpoint, by proclaiming patient satisfaction as their mission, with an underlying emphasis on providing the best possible care for their patients. To do so, the management team must rearrange their infrastructure to reflect patient needs and demands. Satisfaction surveys are a stepping-stone to evaluating customer needs and expectations, thus allowing for the formulation of a policy to accommodate their perspectives. To tackle dissatisfaction issues effectively, the management team needs to establish a strategic plan for evaluating performance. The plan should contain calculated guidelines for each department to follow, by which they can systematically measure their compliance levels. Subsequently, a regular reporting mechanism should be instituted, one that involves department heads, and in turn, the board of directors. Monitoring performance levels helps in understanding how the organization is performing, and how it can operate better in the future.

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HEROIN ADDICTION IN SAUDI ARABIA — NOT MERELY A BEHAVIOURAL PROBLEM

To the Editor: We would like to highlight the importance and the lack of awareness of medical complications resulting from abuse of hard drugs. Almost all previously reported studies in this field from within the Gulf states,[1-6] have shed light on the precipitating factors for addictive behaviour, and its socio-cultural complications, but have paid little if any attention to the serious, sometimes fatal medical complications that may result from abusing or being addicted to these drugs. Such medical complications could prove lethal unless detected early, correctly diagnosed and effectively treated. We have had experience in liaison consultation psychiatry while working at King Fahad General Hospital in Jeddah, Saudi Arabia. In our experience such complications are frequent. We analyzed data on all patients who either attended the emergency rooms or had been admitted to the hospital complaining of a medical problem recognised to result from the abuse of heroin. In a relatively short period of time (six months) the authors assessed and treated 48 addicted patients, including 45 males and 3 females, who complained primarily of a medical problem related to their drug abuse. The medical complications according to sociodemographic characteristics of the 45 male patients are shown in Table 1. Two of the 48 died in the hospital due to complications, one a female with severe bilateral deep vein thrombosis complicated with pulmonary embolism and the other a male, who died with renal failure and myoglobinuria.

Table 1. Medical complications according to sociodemographic factors among 45 male heroin addicts.

Complications	Age (years)		Marital status			Education		Employment	
	≤40	>40	Single (n=16)	Married (n=24)	Divorced (n=5)	Low and Moderate (n=5)	High	Yes	No
Multiple sepsis	10	4	7	5	2	11	3	4	10
Deep vein thrombosis	9	13	10	12	0	16	6	9	13
Systemic infection	5	8	8	4	1	12	1	9	4
Hepatitis	5	7	9	1	2	10	2	7	5
Pseudoaneurysms	2	3	3	0	2	4	1	3	2
Renal failure and myoglubinuria	1	0	1	0	0	0	1	0	1
Total	32	35	38	22	7	53	14	32	25

Table 2. Medical complications according to duration of heroin addiction and daily intake among 45 male heroin addicts.

Complications	Duration of addiction (years)			Daily heroin intake (grams)		
	<2	2-5	>5	<1	2-5	>5
Multiple sepsis	1	6	7	2	6	6
Deep vein thrombosis	1	10	11	2	13	7
Systemic infection	1	7	5	0	4	9
Hepatitis	1	4	7	1	4	7
Pseudoaneurysms	1	2	2	0	2	3
Renal failure and myoglubinuria	0	1	0	0	0	1
Total	5	30	32	5	29	33

Heroin addiction is a complex and rather poorly understood social as well as medical problem. Besides its overemphasised socio-religious stigma and repercussions, heroin addiction can result in life-threatening medical complications. A non-exhaustive list of these complications includes multiple systemic infections, thrombophlebitis, deep vein thrombosis, hepatitis, HIV, acute pulmonary oedema, rhabdomyolysis, renal failure, and accidental or self-deliberate overdose that may cause death.[7-9] We describe 48 patients with at least 67 serious medical complications that were the result of heroin addiction. All attended one hospital in Jeddah, a city served medically by more than twenty hospitals equipped and able to treat such complications. This number may only reflect and highlight how common and serious medical complications among heroin addicts in Saudi Arabia may be. Though there are no well-controlled epidemiological studies on the incidence and prevalence of these complications,[10-12] the vast majority of studies suggest a high incidence. Our findings suggest an even higher incidence among heroin addicts in the Kingdom. This suggestion gains some support from all previous studies from the Kingdom. Osman et al in 1992 showed that the purity of street heroin in the Kingdom was very low compared to that in western countries, and he predicted more unattended medical complications due to the high level of additives in Saudi street heroin. These additives may be incriminated for the higher incidence of complications. Among our patients, the most serious complications were related to either the length of heroin addiction or of the amount of daily intake of heroin (Table 2). The larger the daily doses and the longer the duration of addiction, the more frequent and serious the complications. When the adverse effects of these two dimensions are compared, however, the amount of daily intake seems to be more serious than the duration of the habit. This suggests that the more fatal complications may indeed be related to the contaminants and additive more than the inherent properties of the heroin itself.

Despite such an alarming high morbidity and mortality among heroin addicts in Saudi Arabia, most if not all published studies from the Kingdom have highlighted and emphasised only precipitating socio-religious factors, with unwarranted neglect to the serious medical complications. Most studies have tried to highlight only the importance of weak religious adherence or social adversity as the most important causative and perpetuating factor for this problem. An overemphasis on these factors may blur other important factors, such as genetic and personal factors that may deter patients from coming forward for treatment in appropriate time. Addictive behaviour is a complex problem whose cause should not be reduced to weak religious adherence or adverse social life events, particularly in a country with a strong religious tradition such as the Kingdom. Strong stigmatisation may compromise the motivation of addicts who may be willing to seek medical help. Notwithstanding the protective role of a strong religious commitment in maintaining and enhancing social well-being and reducing the self-destructive behaviour, we think that a more balanced and sensitive view and approach should be adopted if we are to properly prevent and effectively treat the addiction problem in the Kingdom.

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PULMONARY INTERSTITIAL EMPHYSEMA IN A FULL-TERM INFANT: DO WE KNOW THE INCIDENCE?

To the Editor: With interest I read the article by Husam Salama et al in the May/July 2003 issue of the Annals.[1] The image in Figure 1 is not showing pulmonary interstitial emphysema (PIE), but rather multiple air cystic lesions which could be pneumatocele due to previous pneumonia. Why was meconium aspiration causing pneumonitis not discussed as a possible diagnosis with the presence of the meconium below the vocal cord as mentioned in the article? This might explain the pneumatoceles.

Thank you and best regards.

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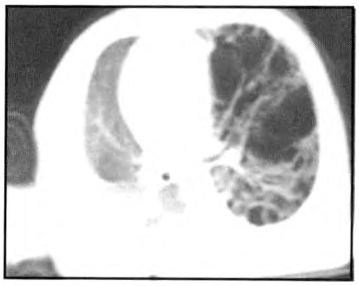

Figure 1. CT scan of the lungs demonstrating extensive degree of pulmonary interstitial emphysema affecting the left lung.

REPLY

To the Editor: Although pneumatocele secondary to meconium aspiration pneumonia is an important differential diagnosis and can happen as early as 48 hours, it is unlikely for the following reasons: the meconium found in both the ligure and below the vocal cords was thin and scanty; the baby deteriorated quickly and developed a radiological picture in the first 24 hours after birth that showed progressive features of PIE (original x-rays are available on request); and the response to selective intubation was dramatic (within less than 48 hours).

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Reference

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World Cancer Report

Edited by Bernard W. Stewart and Paul Kleihues
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World Health Report is part of a series of monographs published under the auspices of World Health Organization and International Agency for Research in Cancer. It is a combined effort by more than 50 contributors from all over the world who have tried to summarize the current knowledge regarding causes and epidemiology of cancer, the molecular basis of carcinogenesis, as well as strategies for cancer prevention and treatment of common cancers encountered around the world.

The book opens with a comprehensive discussion of the global burden of cancer covering the incidence and prevalence of cancer in major regions of the world .The rest of the book is divided into six broad heading each containing several chapters. These headings include: The Causes of Cancer, The Mechanism of Tumor Development, Prevention and Screening, Human Cancers by Organ Sites, Cancer Management, and Cancer Control. The chapters included under these headings provide a comprehensive overview of all aspects of cancer.

The production quality of the monograph is truly outstanding. High quality pictures and diagrams, many of which are in color, richly illustrate all of the chapters. These illustrations are especially helpful in the chapters, that cover the molecular genetics of cancer. The references are also up to date and relevant to the subject matter.

I truly enjoyed reading this book that provides such a wealth of information, which may not be easily available in any one book dealing with cancer. The chapters dealing with the molecular basis of carcinogenesis are full of extremely valuable information and state-of-the-art discussion of this rather complex subject. This I believe is a special appeal and strength of the book. This book is highly recommended for all medical personnel involved with diagnosis, prevention and treatment of cancer particularly oncologists, and pathologists. Reading of this book is a must for the trainees in these specialties.

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Updated Interim U.S. Case Definition for Severe Acute Respiratory Syndrome (SARS)

The previous CDC SARS case definition (published July 16, 2003) has been updated as follows:

- The Exclusion Criteria have been revised to allow exclusion of cases with a convalescent-phase serum sample (i.e., collected >28 days after symptom onset) that is negative for antibody to SARS-associated coronavirus (SARS-CoV). Testing results from serum previously collected between 22 and 28 days after symptom onset are acceptable and will not require collection of an additional sample >28 days after symptom onset.
- The Case Classification has been revised to exclude probable and suspect SARS cases with convalescent-phase serum samples that are negative for antibody to SARS-CoV.

Clinical Criteria

- Asymptomatic or mild respiratory illness
- Moderate respiratory illness
  - Temperature of >100.4°F (>38°C)*, and
  - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia).
- Severe respiratory illness
  - Temperature of >100.4°F (>38°C)*, and
  - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), and radiographic evidence of pneumonia, or respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

Epidemiologic Criteria

- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community transmission of SARS (see Table below), or
- Close contact[§] within 10 days of onset of symptoms with a person known or suspected to have SARS.

The last date for illness onset is 10 days (i.e., one incubation period) after removal of a CDC travel alert. The case patient's travel should have occurred on or before the last date the travel alert was in place.

Table. Travel criteria for suspect or probable U.S. cases of SARS.

Area	First date of illness onset for inclusion as reported case[‡]	Last date of illness onset for inclusion as reported case[†]
China (Mainland)	November 1, 2002	July 13, 2003
Hong Kong	February 1, 2003	July 11, 2003
Hanoi, Vietnam	February 1, 2003	May 25, 2003
Singapore	February 1, 2003	June 14, 2003
Toronto, Canada	April 1, 2003	July 18, 2003
Taiwan	May 1, 2003	July 25, 2003
Beijing, China	November 1, 2002	July 21, 2003

Laboratory Criteria[¶]

- Confirmed
  - Detection of antibody to SARS-associated coronavirus (SARS-CoV) in a serum sample, or
  - Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or
  - Isolation of SARS-CoV.
- Negative
  - Absence of antibody to SARS-CoV in a convalescent–phase serum sample obtained >28 days after symptom onset.**
- Undetermined
  - Laboratory testing either not performed or incomplete.

Case Classification***

- Probable case: meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.
- Suspect case: meets the clinical criteria for moderate respiratory illness of unknown etiology, and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.

Exclusion Criteria

A case may be excluded as a suspect or probable SARS case if:

- An alternative diagnosis can fully explain the illness.****
- The case has a convalescent-phase serum sample (i.e., obtained >28 days after symptom onset) for which is negative for antibody to SARS-CoV.**
- The case was reported on the basis of contact with an index case that was subsequently excluded as a case of SARS, provided other possible epidemiologic exposure criteria are not present.

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*A measured documented temperature of >100.4°F (>38°C) is preferred. However, clinical judgment should be used when evaluating patients for whom a measured temperature of >100.4°F (>38°C) has not been documented. Factors that might be considered include patient self-report of fever, use of antipyretics, presence of immunocompromising conditions or therapies, lack of access to health care, or inability to obtain a measured temperature. Reporting authorities should consider these factors when classifying patients who do not strictly meet the clinical criteria for this case definition.

§Close contact is defined as having cared for or lived with a person known to have SARS or having a high likelihood of direct contact with respiratory secretions and/or body fluids of a patient known to have SARS. Examples of close contact include kissing or embracing, sharing eating or drinking utensils, close conversation (<3 feet), physical examination, and any other direct physical contact between persons. Close contact does not include activities such as walking by a person or sitting across a waiting room or office for a brief period of time.

‡ The WHO has specified that the surveillance period for China should begin on November 1; the first recognized cases in Hong Kong, Singapore and Hanoi (Vietnam) had onset in February 2003. The date for Toronto is linked to the occurrence of a laboratory confirmed case of SARS in a U.S. resident who had traveled to Toronto; the date for Taiwan is linked to CDC's issuance of travel recommendations.

†The last date for illness onset is 10 days (i.e., one incubation period) after removal of a CDC travel alert. The case patient's travel should have occurred on or before the last date the travel alert was in place.

¶Assays for the laboratory diagnosis of SARS-CoV infection include enzyme-linked immunosorbent assay, indirect fluorescent-antibody assay, and reverse transcription polymerase chain reaction (RT-PCR) assays of appropriately collected clinical specimens (Source: CDC. Guidelines for collection of specimens from potential cases of SARS. Available at www.cdc.gov/ncidod/sars/specimen_collection_sars2.htm). Absence of SARS-CoV antibody from serum obtained <28 days after illness onset, ** a negative PCR test, or a negative viral culture does not exclude SARS-CoV infection and is not considered a definitive laboratory result. In these instances, a convalescent serum sample obtained >28 days after illness is needed to determine infection with SARS-CoV. ** All SARS diagnostic assays are under evaluation.

**Does not apply to serum samples collected before July 11, 2003. Testing results from serum samples collected before July 11, 2003 and between 22 and 28 days after symptom onset are acceptable and will not require collection of an additional sample >28 days after symptom onset.

*** Asymptomatic SARS-CoV infection or clinical manifestations other than respiratory illness might be identified as more is learned about SARS-CoV infection.

**** Factors that may be considered in assigning alternate diagnoses include the strength of the epidemiologic exposure criteria for SARS, the specificity of the diagnostic test, and the compatibility of the clinical presentation and course of illness for the alternative diagnosis.

IRIN
INTEGRATED REGIONAL INFORMATION NETWORK

Using cell phones to fight TB

JOHANNESBURG, 14 April (IRIN) - A pilot project in the coastal city of Cape Town is using the text message service on cell phones to remind patients to take their medication, saving the over-stretched public health services time and money. The country is said to be facing one of the worst TB epidemics in the world, with disease rates up to 60 times higher than those currently experienced in the United States.

Treatment for the disease, however, is still a problem. TB patients must strictly follow a difficult drug regime of four tablets, five times a week, for six months. Patients end up being resentful of such an "oppressive" process, project creator Dr David Green, told IRIN.

Consequently, they either forget to take their medication or interrupt their treatment.

"This is a significant problem because they become more resistant to the treatment and MDR [multidrug resistant] TB is more expensive to treat," Green said.

But now up to 300 patients in a local clinic in Cape Town have been receiving a text message on their cell phones reminding them to take their pills. Of the patients involved in the project, there has been only one treatment interruption.

When patients complained that the initial message "take your medicine now" was too "boring", Green added disease information and tips about lifestyle management.

"After a month of being on treatment, the service would send a message warning the patient that even though they were feeling better, they had to continue with the treatment," he said.

The initiative uses technology in a simple, cheap and flexible way: a software application captures the patient's details into a database, a computer server reads the database, and then sends personalised messages to each patient.

At a relatively inexpensive US $1.5 per patient per month for th e short message service (SMS) reminder, the local health authority has decided to extend the pilot project to other clinics with high cell phone ownership.

"Clearly if more people are likely to finish their treatment on SMS technology, it will save the health department a lot of money and it will relieve the burden on our health system," Green noted.

Health experts were initially sceptical whether the uptake of cell phone technology was high enough to justify the project.

Research into cell phone ownership, however, found that one in three people with TB in the township of Khayelitsha had cell phones. "Even the very poor have cell phones these days, that is no longer an excuse," Green said. At the clinic where the pilot study was conducted, 71 percent of TB patients had access to a cell phone.

Medical experts have cautiously welcomed the project. "Its certainly an interesting and novel way to fight a major problem," Dr Karen Weyer, director of the Medical Research Council (MRC) TB Unit, said.

But an increase in adherence could only be tested by randomised control trials, she noted. The MRC and the University of Cape Town will embark on trials to compare the effectiveness of the SMS reminder service against the cost of non-compliance to TB treatment.

In the meantime, more TB patients in Cape Town will be reminded that TB is curable – with regular treatment.

The Integrated Regional Information Network (IRIN) manages a flexible and up-to-date feed of information to and from non-governmental agencies (NGOs), national authorities, UN agencies, donors, human rights organisations, political parties, regional institutions, churches, academia, businesses and the media. The IRIN covers sub-Saharan Africa, the Caucasus, and Central Asia, regions that are often under-reported, misunderstood, or ignored. By fostering greater awareness and understanding of regional issues and events, the IRINs contribute to better-informed and more effective humanitarian action and media coverage, including emergency preparedness and advocacy.

FELLOWSHIPS AND TRAINING PROGRAMS

Pediatric Neurology Fellowship Program

King Faisal Specialist Hospital and Research Centre invites applicants for its Pediatric Neurology Fellowship Program. This is a 3-year fellowship training program, with two years spent in Riyadh and one year abroad. Applicants must have successfully completed training in an accredited residency training program, and successfully passed the Pediatric Arab Board certifying exam or its equivalent. For further information, please contact Academic and Training Affairs, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-464-7272, ext. 31834; fax: (966) 1-442-7237.

Postgraduate Training Program in Anesthesiology

The Anesthesiology Department of King Faisal Specialist Hospital and Research Centre is pleased to invite applications for its postgraduate training program in Anesthesiology. The course will involve one year of training at KFSH&RC, and a four-year residency training period in North America. For further information, please contact: Academic and Training Affairs, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-442-7215; fax: (966) 1-442-7237.

SEMINARS, TRAININGS & WORKSHOPS

Spatial and Temporal Clustering of Diseases and Risk Assessment in Public Health

The Academic & Training Affairs in coordination with Biostatistics, Epidemiology and Scientific Computing of King Faisal Specialist Hospital & Research Centre wishes to announce its "Spatial and Temporal Clustering of Diseases and Risk Assessment in Public Health" which will be held on 9-10 December 2003.

For further information, contact: Academic & Training Affairs, KFSH&RC, MBC 36, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) 1-442-7238; fax: (966) 1-442-4153, (966) 1-442-7237; e-mail: web_symposia@kfshrc.edu.sa. Website: www.kfshrc.edu.sa/symposia.

15th Scientific Session of the Saudi Heart Association

The Saudi Heart Association will hold its annual meeting on 6-8 January 2004 in Intercontinental Hotel, Jeddah, Saudi Arabia.

This conference will bring cardovascular experts and specialist from aroung the world to discuss latest issues and findings in cardiovascular medicine.

Distinguished international speakers, in addition to large number of local speakers are invited to give lectures about topics concerning cardiovascular medicine.

There will also be a major contribution to the meeting by local experts from different cardiovascular centers in the Kingdom.

There will be 4 workshops on Echo-1 Adult, Echo-1 Pediatric, ECG & Advance Arrhythmia and Congenital Pathology.

For further information, please contact the Saudi Heart Association's Office, College of Medicine, King Saud University, P.O. Box 2925 Riyadh 11461 Saudi Arabia. Tel: 1-467-1434; Fax: 1-467-2553; e-mail: saudhass@ksu.edu.sa.

Workshop on Research Writing

The Bahrain Medical Bulletin in cooperation with the International Corporation of Research Editing and Design wishes to announce its "Workshop on Research Writing" which will be held on 04 December 2003 at the Araban Gulf University, Kingdom of Bahrain.The workshop is open to participants of all biomedical specialties. It is limited to 30 participants only.

Topics for discussion include: The Art of Writing, Research Design, Statistical Analysis, How to do Research and Generate Ideas, Ethics of Research, Structure of Scientific Paper, Analysis of applied Research Exercise.

For inquiries, please contact The Secretary, Bahrain Medical Bulletin, P.O. Box 32159, Kingdom of Bahrain.Tel: (973)239798; Fax:(973) 277036;Email: bahmb@batelco.com.bh.

ERRATA

Vol 23;3-4 (May/July 2003)

In the letter to the editor "Congenital anomalies of the kidneys in family members," the names of the following authors should have appeared: Mehmet Cimen, Mursit Acemoglu, Sebati Erdil, Ferda Percin.

Vol. 23;5 (September/October 2003)

"Type II diabetes and its association with hypertension and depression in an Iraqi population" On page 256, in Table 2, statistical significance vs. controls should have been indicated for mid-upper arm muscle area for males (36.0±9.0 vs. 45.45±22.7; $P<0.01$) and for waist-to-hip circumference for females (0.95±0.073 vs. 0.90±0.086; $P<0.01$). In the footnote, $P>0.05$ should have been $P<0.05$. On page 257, in the footnote to Table 4, $P<0.01$ should have read $P<0.001$.

HEALTH/MEDICAL EVENTS 2004

SAUDI ARABIA

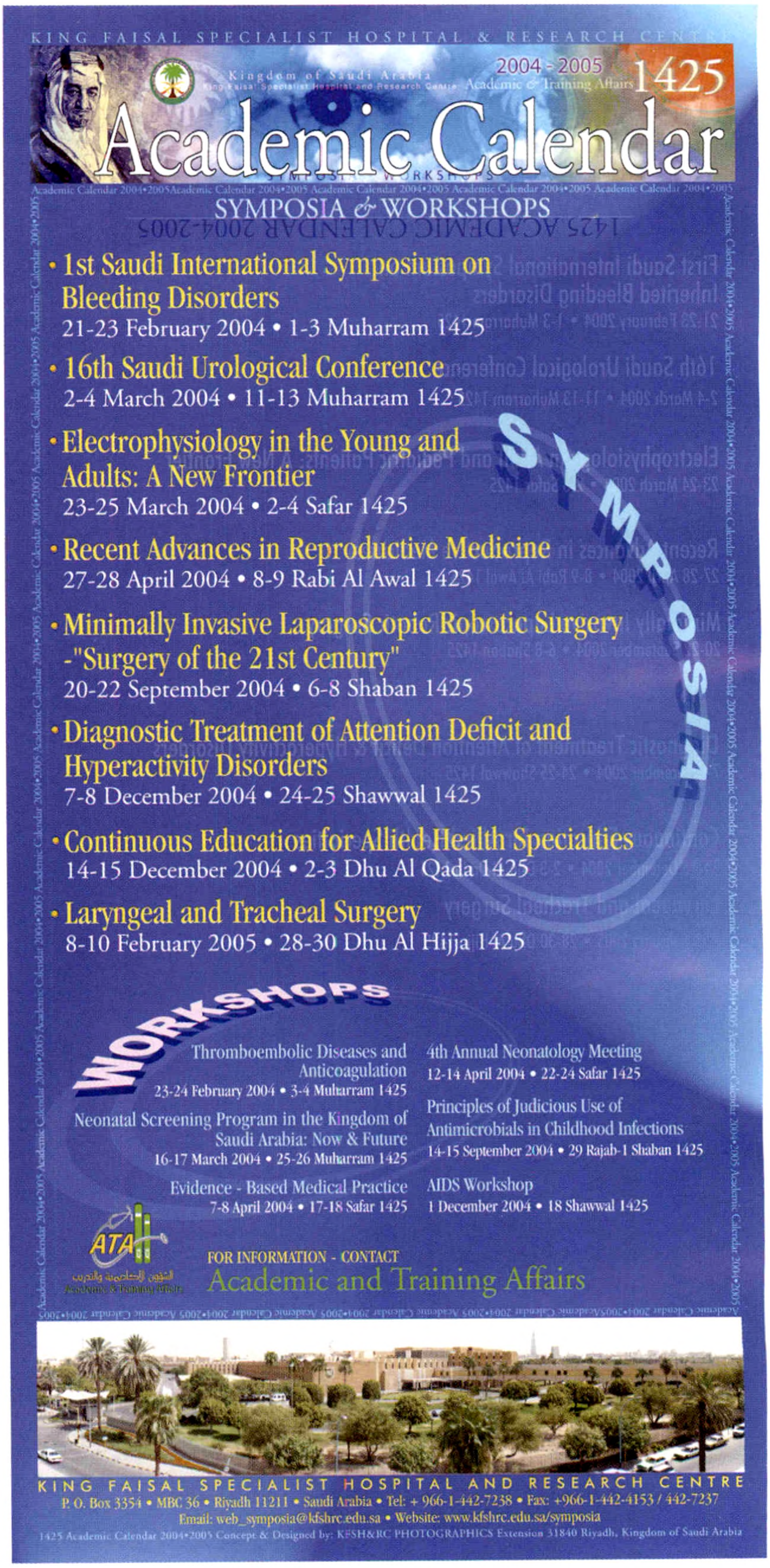
25-27 February
The 2nd Annual Conference of the Saudi Thoracic Society
Dammam
Contact info:
Tel: 00-96-612-781-960
Fax: 00-96-614-679-496
Email: mshajjaj@mail.com

28 February-02 March
5th Pan Arab Congress On Endocrinology and Diabetes
Riyadh
Contact Info:
Tel: 00-96-614-786-100 ext. 5162
Fax: 00-96-614-775-696
Email: panarabcongress5@hotmail.com

29 February-02 March
4th RKH Paediatric Symposium: Paediatric Nephrology & General Paediatrics Update
Riyadh
Contact info:
Tel: 00-96-614-791-000 ext. 5452
Fax: 00-96-614-791-000 ext 3235
Email: smohaimeed@hotmail.com

16-18 March
International Conference on Advances in Internal Medicine
Jeddah
Contact info:
Tel: 00-96-626-240-000 ext. 1244
Fax: 00-96-626-240-000 ext. 1009
Email: alemsm@ngha.med.sa

21-22 March
6th Middle East Symposium on Anaesthesia for the Cardiac Patient
Riyadh
Contact info:
Tel: 00-96-614-791-000 EXT. 8554
Fax: 00-96-614-760-543
Email: anesthesia@pscc.med.sa



KING FAISAL SPECIALIST HOSPITAL & RESEARCH CENTRE

Kingdom of Saudi Arabia
King Faisal Specialist Hospital and Research Centre
2004 - 2005
Academic & Training Affairs 1425

Academic Calendar

SYMPOSIA & WORKSHOPS

- 1st Saudi International Symposium on Bleeding Disorders
  21-23 February 2004 • 1-3 Muharram 1425
- 16th Saudi Urological Conference
  2-4 March 2004 • 11-13 Muharram 1425
- Electrophysiology in the Young and Adults: A New Frontier
  23-25 March 2004 • 2-4 Safar 1425
- Recent Advances in Reproductive Medicine
  27-28 April 2004 • 8-9 Rabi Al Awal 1425
- Minimally Invasive Laparoscopic Robotic Surgery -"Surgery of the 21st Century"
  20-22 September 2004 • 6-8 Shaban 1425
- Diagnostic Treatment of Attention Deficit and Hyperactivity Disorders
  7-8 December 2004 • 24-25 Shawwal 1425
- Continuous Education for Allied Health Specialties
  14-15 December 2004 • 2-3 Dhu Al Qada 1425
- Laryngeal and Tracheal Surgery
  8-10 February 2005 • 28-30 Dhu Al Hijja 1425

SYMPOSIA

WORKSHOPS

Thromboembolic Diseases and Anticoagulation
23-24 February 2004 • 3-4 Muharram 1425

Neonatal Screening Program in the Kingdom of Saudi Arabia: Now & Future
16-17 March 2004 • 25-26 Muharram 1425

Evidence - Based Medical Practice
7-8 April 2004 • 17-18 Safar 1425

4th Annual Neonatology Meeting
12-14 April 2004 • 22-24 Safar 1425

Principles of Judicious Use of Antimicrobials in Childhood Infections
14-15 September 2004 • 29 Rajab-1 Shaban 1425

AIDS Workshop
1 December 2004 • 18 Shawwal 1425

ATA
الشؤون الأكاديمية والتدريب
Academic & Training Affairs

FOR INFORMATION - CONTACT
Academic and Training Affairs

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE
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Email: web_symposia@kfshrc.edu.sa • Website: www.kfshrc.edu.sa/symposia
1425 Academic Calendar 2004•2005 Concept & Designed by: KFSH&RC PHOTOGRAPHICS Extension 31840 Riyadh, Kingdom of Saudi Arabia

GULF

01 January
30th Annual Meeting of the European Thyroid Association
Istanbul, Turkey
Contact info:
Tel: 90-312-309-4717
Fax: 90-312-310-5350
Email: president@semt.org.tr

12-15 January
Second Gulf Heart Association Conference
Muscat, Oman
Contact Info:
Email: secretary@gha04.org
Website: www.gha04.org

18-21 January
Arab Health 2004 Congress
Dubai, UAE
Contact info:
Tel: 971-4-3365161
Fax: 971-4-3364021
Website: www.iirdubai.com

20-22 February
The 1st Pan-African & Pan-Arab International Pediatric Epilepsy Conference
Cairo, Egypt
Contact Info:
Tel: 011-202-3922-585
Fax: 011-202-3922-585
Email: enps@hotmail.com/ info@enps-eg.com
Website: www.enps-eg.com

23-25 February
1st International Physiotherapy and Rehabilitation Conference
Muscat, Oman
Contact info:
Tel: 00-968-515-708
Fax: 00-968-515-708
Email: physio@squ.edu.om

03-05 March
Hot Topics in Neonatology
Sharm El Sheikh, Egypt
Contact info:
Tel: 002-026-383-656
Fax: 002-022-660-717
Email: gamal@internetegypt.com

04-07 March
Multidisipliner approachs in otolaryngology-head and neck surgery
Bursa, Turkey
Contact info:
Tel: 90-2-244-428-303
Fax: 90-2-244-428-091
Email: kbb@uludag.edu.tr

GULF

7-11 March
The 2nd International Trauma Care, Disaster & Emergency Medicine Conference
Doha, Qatar
Contact Info:
Email: emergency@hmc.org.qa
Website: www.hmc.org.qa17-20 March 2004
14th Congress of the European Urological Association
Istanbul, Turkey
Contact info:
Tel: 31-0-263-890-680
Fax: 31-0-263-890-674
Email: eau@uroweb.nl

23-26 March
8th Pan Arab Conference of Diabetes PACD8
Cairo, Egypt
Contact info:
Tel: 20-122-131-868
Fax: 20-22-723-693
Email: mahmoud@arab-diabetes.com

29-31 March
Anti-Aging Middle East
Dubai, UAE
Contact info:
Tel: 971-4-3329029
Fax: 971-4-3329648
Email: mail@antiagingmiddleeast.com
Website: www.antiagingmiddleeast.com

02-04 April
1st Mediterranean Congress of Neurology
Nicosia, Cyprus
Contact info:
Tel: 35-725-720-554
Fax: 35-725-721-644
Email: medneuro2004@congresswise.com

OTHER COUNTRIES

19-23 January
Review and Update in Pediatric Emergency Medicine
Sarasoto, Florida, USA
Contact info:
Website: www.ams4cme.com/www/brochure/calendar.aspx

19-20 January
Dermatologic Procedures
Midland, Michigan, USA
Contact Info:
Website: www.npinstitute.com/courses.html

23-27 January
XI International Congress of Ocular Oncology
Hyderabad, India
Contact info:
Website: www.eyetumors.com

30 January-02 February
Toward a Defining Moment: Insulin Resistance Syndrome
Paradise Island, Bahamas
Contact Info:
Website: www.iirs.org

02-06 February
Geriatrics: Issues in Primary Care Medicine
Sarasoto, Florida, USA
Contact info:
Website: www.ams4cme.com

05-07 February
Heart, Rheumatology and Autoimmunity
Milan, Italy
Contact info:
Website: www.oic.it/home/congresses/framecngr.htm

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Switzerland

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لوزان – سويسرا

1st Saudi International Symposium on BLEEDING DISORDERS

21-23 February 2004 / 01-03 Muharram 1425

CALL for ABSTRACTS

CME accredited

TOPICS:

- Hemophilia and Its Complications
- Molecular Aspects of Bleeding Disorders
- Platelet Disorders
- Von Willebrand's Disease

INFORMATION:

Academic & Training Affairs
MBC 36 - CME Conference Section
King Faisal Specialist Hospital & Research Centre
P.O. Box 3354
Riyadh 11211 Kingdom of Saudi Arabia
Tel: 966-1-442-7238 Fax: 966-1-442-4153
Website: www.kfshrc.edu.sa/symposia
Email: web_symposia@kfshrc.edu.sa

ABSTRACT FORM

"The 1st Saudi International Symposium on Bleeding Disorders"
21-23 February 2004/ 01-03 Muharram 1425

Abstracts will be evaluated by the Scientific Selection Committee and selected on the basis of originality, validity, significance and relevance to the Symposium.

Office Use:
No. ____________

____

DEADLINE FOR SUBMISSION:

10 December 2003

TITLE:

ABSTRACT:

TOPIC SELECTION:

- ☐ Hemophilia Diagnosis & Management
- ☐ Platelet Disorders
- ☐ Von Willebrand's Disease
- ☐ Molecular Aspects of Bleeding Disorders
- ☐ Other

PRESENTATION FORMAT:

☐ Oral ☐ Poster

The Scientific Committe reserves the right to designate an accepted abstract as platform or poster presentation.

EQUIPMENT NEEDED:

- ☐ Single Slide
- ☐ Double Slide
- ☐ VHS/Beta/U-matic
- ☐ X-Ray Projector
- ☐ Desktop Presentation (PC/MAC)

DISCLOSURE:

Has this work been previously presented?

☐ Yes ☐ No

IMPORTANT INFORMATION:

Submission of an abstract constitutes a commitment by the author/s to present the abstract as accepted. Expenses associated with the preparation, submission, and presentation of an abstract are the responsibility of the presenting author/s.

SUBMIT ABSTRACT PLUS THREE PHOTOCOPIES TO:

Conference Coordinator, MBC 36
Academic & Training Affairs
King Faisal Specialist Hospital & Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Tel. No.: +966-1-442-7238
Fax No.: +966-1-442-4153/ 442-7237

Email: web_symposia@kfshrc.edu.sa
Website: www.kfshrc.edu.sa/symposia

FIRST AUTHOR'S DETAILS: ☐ PhD ☐ MD ☐ MSc ☐ Student ☐ Other

NAME: ____________________

INSTITUTION: ____________________

ADDRESS: ____________________

TELEPHONE: ____________ **FAX:** ____________

EMAIL: ____________ **SIGNATURE:** ____________

انتشار متلازمة سابق الحيض والتنبؤ بها بين شابات في عمر الجامعة في المملكة العربية السعودية

الخلفية: تندر البحوث في عوامل خطورة الإصابة بمتلازمة سابق الحيض في دول الخليج بمنطقة الشرق الأوسط، وهي منطقة ذات سمات ثقافية خاصة من الممكن أن تؤثر على توقعات الحالة والإدراك الذاتي له. قمنا بدراسة العلاقة بين تكرار حدوث متلازمة سابق الحيض وعوامل الخطر المحتملة للإصابة بالداء.

والطرق: باستخدام استبيان شخصي، أجرينا مسحاً شمل جميع الشابات المؤهلات من الملتحقات ببرامج طبية أو تمريضية أو تقنية طبية تمريضية / أو برامج تعليمية عن العلاج التنفسي في إحدى الجامعات بالدمام. سئلت المشاركات عن مدى تكرار حدوث الأعراض خلال الشهور الستة الماضية. وأجري تحليل تراجعي متعدد على مراحل بغية تحديد أي من العوامل الحيوية النفسية والتغذوية المختلفة يؤثر على حاصل مجموع أعراض متلازمة سابق الحيض.

النتائج: تعرضت ٤٤٨ امرأة (٩٦,٦%) لعرض واحد على الأقل من أعراض سابق الحيض، بينما أحرزت ١٧٦ منهن (٣٧,٥) درجة عالية على حاصل شدة الأعراض. تبين وجود علاقة كبيرة بين تكرار حدوث أعراض سابق الحيض وتاريخ طبي لدى الأم لمتلازمة سابق الحيض، والإدراك الذاتي للإجهاد الذهني، والنشاط الجسدي، واستهلاك الأطعمة حلوة المذاق، والقهوة، إلاّ أن هذه العوامل لم تفسّر إلا ١٤% فقط من التغيرّية في نموذج التحليل التراجعي المتعدد.

الخلاصة: نوصي النساء المعرضات للإجهاد الذهني بإتباع تقنيات الاسترخاء والأدوية النفسية. علاوة على أن بإمكان الشابات المصابات بمتلازمة سابق الحيض حذف تناول الحلويات والمشروبات المحتوية على الكافيين والقهوة بشكل خلص من نظامهن الغذائي.

الكلمات الرئيسة: متلازمة سابق الحيض، مشروبات بالكافيين، شوكولاتة، كاكاو، تمارين بدنية، إجهاد ذهني، المملكة العربية السعودية.

المدونات الطبية السعودية ٢٣; ٦: ٣٨١-٣٨٧

مضادات الخميرة نازعة الكاربوكسيل لحمض الغلوتامي لدى مرضى السكري من النوع (١) وإخوالهم في سوريا والأردن

الخلفية: أظهرت محاولات التعرف على المراحل المبكرة في داء السكري من النوع (١) بأن نازعة كاربوكسيل حمض الغلوتامي (GAD) هو أحد أهم الأجسام المضادة. وقد قمنا بهذه الدراسة من أجل تحديد مدى انتشار الأجسام المضادة لنازعة كاربوكسيل حمض الغلوتامي (anti-GAD) لدى الأطفال السوريين والأردنيين الذين يعانون من داء السكري من النوع (١) وأخوالهم.

الطرق: تم الحصول على أمصال من ٨٥ مريض سوري مصاب بداء السكري من النوع (١) (متوسط العمر، ٥,٩ ± ١٣,٦ سنوات)، ومن ٤٥ من إخوالهم (متوسط العمر، ٦,١ ± ١١,٣ سنوات)، ومن ٧٨ شخص شاهد سوري تم اختيارهم عشوائياً (متوسط العمر ٤٣ ± ٩ر٩ سنوات)، ومن ٩٥ مريض أردني مصاب بداء السكري من النوع (١) (متوسط العمر ٦٥ ± ١٣,٩ سنوات)، ومن ٧٨ من أشقائهم (متوسط العمر ٧,١ ± ١٢,٣ سنوات)، ومن ١٠٠ شخص شاهد أردني تم اختيارهم عشوائياً (متوسط العمر ٤,٥ ± ٧,٨ سنوات). تم تحليل الأمصال للأجسام المضادة لنازعة الكاربوكسيل باستخدام طريقة (ELISA).

النتائج: مدى انتشار الأجسام المضادة لنازعة الكاربوكسيل هو ٣٤,١% (٢٩/٨٥) مريض سوري يعاني من داء السكري من النوع (١)، ٢٠% (٩/٤٥) من إخوالهم، ١,٣% (١/٧٨) شخص شاهد سوري، ٤٩,٥% (٤٧/٩٥) مريض أردني مصاب بداء السكري (١)، ٢٣% (١٨/٧٨) من إخوالهم، و ٢% (٢/١٠٠) شخص شاهد أردني. كان الفرق واضحاً إحصائياً بين مجموعة المصابين من المرضى السوريين والأردنيين وإخوالهم والمجموعات الشاهدة. كان التكرار بنسبة ٨٨,٨% (١٦/١٨) في المجموعتين لدى المرضى المصابين بداء السكري منذ أقل من سنتين. ولم يكن هنالك ترابط بين الجنس ومستوى الأجسام المضادة لدى مرضى السكري (١) من السوريين والأردنيين وإخوالهم. تميل إيجابية الأجسام المضادة إلى التكرار في عمر ٥-٨ سنوات لدى الأخوان. كان عيار الأجسام المضادة لنازعة الكاربوكسيل أكثر من ٩٠ نانوجرام/ ميليلامبيرت لدى ٥٨,٨% من المرضى المصابين بداء السكري (١) و ٣٨% من إخوالهم كانوا إيجابيين للأجسام المضادة لنازعة الكاربوكسيل .

الخاتمة: مدى انتشار الأجسام المضادة لنازعة كاربوكسيل حمض الغلوتامي لدى المرضى المصابين بداء السكري (١) من السوريين والأردنيين وإخوالهم هو الأعلى في العالم. وبذلك تكون الأجسام المضادة لنازعة كاربوكسيل حمض الغلوتامي مؤشراً مبكراً لداء السكري من النوع (١).

المدونات الطبية السعودية ٢٣; ٦: ٣٧٦-٣٨٠

تكرار ظهور الأضداد الذاتية ومستوياتها لدى جمهور العمانيين الأصحاء البالغين

خلفية الدراسة: أظهرت دراسة سابقة تكراراً مرتفعاً لظهور الأضداد الذاتية لدى المتبرعين بالدم والنساء الحوامل من العمانيين. وقد أجرينا هذه الدراسة الموسعة لتقصي مدى تكرار ظهور الأضداد الذاتية المتعددة وأهمية ذلك لدى الأفراد الأصحاء من مناطق مختلفة في عمان.

المرضى والطرق: تم جمع أمصال من ١٥٣٧ عماني يتمتعون بصحة جيدة (١١٥٣ رجل و ٣٨٤ امرأة) وتتراوح أعمارهم من ١٨–٥٧ سنة، وتم تحليلها بحثاً عن عشرة أضداد ذاتية مختلفة باستخدام التألق المناعي غير المباشر، والتراص الدموي، وتراص اللاتكس.

النتائج: ظهرت مستويات منخفضة من الأضداد الذاتية لدى ٣٣,٥%، بينما ظهرت مستويات مرتفعة من الأضداد الذاتية لدى بضعة أفراد آخرين (١,٨%). كانت الأضداد الذاتية للعضلات الملساء هي الأكثر وضوحاً (١١%). وجاء في المرتبة الثانية الأضداد للنواة (٧,٦%). وكان وجود الأضداد الذاتية للجسيمات الصغيرة الدرقية والأضداد الذاتية لغلوبلين الدرقية هو بنسبة ٦,٥% و ٤ر٤% لدى الأفراد على التوالي. كان تكرار الأضداد الذاتية الأخرى أقل بكثير : كانت الأضداد الذاتية للخلايا الجدارية في ١,٦%، أضداد حافة الفرشاة في ١,٣%، الأضداد الذاتية للشبكين في ١%، أضداد المتقدرات في ٠,٨%، أضداد الكبيبات في ٠,٧% والعامل الرثوي في ٠,٤%.

الخلاصة: تشير المعلومات إلى وجود الأضداد الذاتية لدى الأفراد العمانيين الأصحاء، لهذا يجب الحذر عند تحليل النتائج المخبرية للمرضى الذين يشك في إصابتهم بداء ذاتي المناعة.

المدونات الطبية السعودية ٢٣; ٦: ٣٧٢-٣٧٥

التغيير الحاصل في نمط التهاب الكبد الفيروسي في المملكة العربية السعودية خلال العقدين الماضيين

مقدمة: تراكمت المعلومات ذات العلاقة بوبائية التهابات الكبد الفيروسية ب وج و أ في المملكة العربية السعودية خلال العقدين الماضيين. نراجع في هذه الدراسة للتغييرات الحاصلة في وبائية هذه الالتهابات، ونقترح استراتيجيات لاستئصالها.

الطرق: بحثنا في المجلات الطبية السعودية وفي ميدلاين عن التقارير المتعلقة بالتهابات الكبد ب وج و أ، وحللنا البيانات الرسمية عن التهابي الكبد ب وج الصادرة من بنك الدم المركزي التابع لوزارة الصحة وبنك الدم التابع لمستشفى الملك خالد الجامعي.

النتائج: أظهرت عدة دراسات من عقد الثمانينات توطن التهاب الكبد ب إذ تراوحت نسبة المصابين من السكان بين ٥% و ١٠%، وكانت نسبة الانتشار تختلف من منطقة إلى أخرى. كانت نسبة الانتشار تبلغ ٧% تقريبا لدى الأطفال (من سنة واحدة إلى ١٢ سنة) في سنة ١٩٨٩م، أي قبيل إضافة لقاح التهاب الكبد ب إلى برنامج التحصين الموسع، ولكنها انخفضت إلى ٠,٣% في سنة ١٩٩٧م. كما أن نتائج فحوص المتبرعين أظهرت هبوطا مطردا في التهاب الكبد ب. ففي مستشفى الملك خالد الجامعي هبطت نسبة الانتشار من ٣,٧% في سنة ١٩٨٧م إلى ١,٧% في سنة ٢٠٠٠م. كذلك انخفض التهاب الكبد ج كثيرا، ويرجع ذلك جزئيا إلى تحسن الفحوص التشخيصية، ولكن انتقال هذا الالتهاب ما زال مستمرا بين السعوديين. ومع أن التهاب الكبد أ آخذ في الهبوط إلا أن معدلات الإصابة ما زالت مرتفعة في بعض المناطق. ففي سنة ١٩٩٧م كان هناك دليل مصلي على هذا الالتهاب لدى ما نسبته ٢٥% من الأطفال.

الاستنتاج: لقد ساهمت استراتيجية وزارة الصحة للوقاية من التهاب الكبد الفيروسي في المملكة العربية السعودية في خفض معدلات انتشاره بدرجة ملحوظة، وينبغي الاستمرار في هذه الاستراتيجية. ينبغي أيضا مراقبة سياسات مكافحة العدوى في المراكز الصحية والمستشفيات بصورة دقيقة، وهناك حاجة إلى مزيد من التوعية الصحية وإلى أنظمة صحية وأنظمة مياه شاملة في جميع مناطق المملكة.

المدونات الطبية السعودية ٢٣; ٦: ٣٦٧-٣٧١

توزع كل من الأميبا الحالّة للنُسجُ عن الأميبا المتخالفة وتشخيصها التفريقي باستخدام طريقة تفاعل البلمرة المتسلسلة – تعدد أشكال طول القطع المجزأة في وسط إيران

الخلفية: إن الأميبا الحالة للنُسجُ والأميبا المتخالفة طفيليان بشريان من الأولي يتعذر التمييز بينهما بالشكل، وهما مختلفان من الناحية الوراثية. يمكن التفريق بين الأميبا الحالّة للنُسجُ الكامنة والممرضة وبين الأميبا المتخالفة الطفيلية التي لا تغزو النسج بواسطة طرق جزيئية وطرق أخرى. استخدمنا طريقة تفاعل البلمرة المتسلسل لتحديد نسبة وقوع النوعين بين مواطني طهران وكراج في وسط إيران.

المرضى والطرق: تم جمع عينات براز بشرية عشوائياً في كل من طهران وكراج، أجريت فحوص كيسات الأميبا الحالّة للنُسجُ والأميبا المتخالفة بطرق مباشرة وايثر-فورمالين (N=١٢١٤٨). جاءت نتيجة ٧٨ حالة إيجابية (٠,٧%)، وتم بنجاح إجراء مزرعة لـ ٤٩ حالة معزولة منها في مستنبت روبنسون. استخدمنا كمحفزات زوجين من سلسلة من بضع نويدات تم تصميمها من بيانات تسلسل الدنا DNA المجينة للمستضد السطحي (٢٣٠ دالتون) في الأميبا الحالّة للنُسجُ / والأميبا المتخالفة في تضخيم ٣٧٤ جزءاً من الأسس القاعدية. وتم إحلال الأنماط الرحلانية كهربائية لناتج تفاعل البلمرة المتسلسل بواسطة إنزيم هنفل الحصري، والذي استخدم للتفريق بين النوعين.

النتائج: إن نمط أشكال طول القطع المجزأة (RFLP) والذي تم الحصول عليه من أميبا حالّة للنُسجُ قياسية ومعزولة، فيه قطعتان أطوالها (٢١٩ زوج من الأسس القاعدية و ١٥٥ زوج من الأسس القاعدية)، لكن الأميبا المتخالفة المعيارية المعزولة أظهرت ثلاثة قطع أطوالها ١٥٥، ١٥٢، ٦٧ زوجاً من الأسس القاعدية). أظهر التشخيص التفريقي لـ ٤٩ حالة عزل للأميبا الحالّة للنُسجُ / والأميبا المتخالفة من طهران وكراج باستخدام تفاعل البلمرة المتسلسل – ونمط أشكال طول القطع المجزأة (RFLP) أن ٤٦ (٩٣,٩%) كانوا أميبا متخالفة، بينما اثنان فقط (٤,١%) كانوا أميبا حالّة للنُسجُ. شخص واحد (٢%) كان مصاباً بالتهاب مختلط وظهر لديه النمطان كلاهما.

الخاتمة: يشكل التشخيص التفريقي للطفيليات الكامنة والممرضة للأميبا الحالّة للنُسجُ وللأميبا المتخالفة وغير الممرضة أهمية سريرية ووبائية. تثبت هذه الدراسة أن الأميبا المتخالفة منتشرة أكثر بكثير من الأميبا الحالّة للنُسجُ فيما بين "من يطرحون كيسات الأميبا" في طهران وكراج في وسط إيران.

الكلمات الرئيسة: أميبا حالّة للنُسجُ، أميبا متخالفة، تفاعل البلمرة المتسلسل – تعدد أشكال طول القطع المجزأة، إيران.

المدونات الطبية السعودية ٢٣; ٦: ٣٦٣-٣٦٦

السلمونيلة كجرثومة مسببة لمختلف الالتهابات في مرضى الخلايا المنجلية

خلفية الدراسة: مرضى الخلايا المنجلية معرضون للإصابة بمختلف الالتهابات الجرثومية، بما في ذلك الالتهابات الناجمة عن أنواع السلمونيلة. حاولنا التعرف على أكثر الالتهابات شيوعاً التي تسببها السلمونيلة في مرضى الخلايا المنجلية في مستشفانا، وتحديد معدلات وفياتهم ومدى تأثير العقاقير المضادة للجراثيم الأكثر شيوعاً عليهم.

المرضى والطرق: أجرينا دراسة استطلاعية على جميع الالتهابات بالسلمونيلة في مرضى الخلايا المنجلية الذين أدخلوا إلى مستشفى القطيف المركزي خلال السنوات الإحدى عشرة الماضية.

النتائج: خلال السنوات الإحدى عشرة الماضية، حدثت ٣٣١ التهاباً بالسلمونيلة في ٣١٩ مريضاً. بلغت نسبة الإصابة بالتهاب السلمونيلة في مرضى الخلايا المنجلية ١١,٥% مقارنة بنسبة ٠,٦٥% فقط في بقية مرضى المستشفى. كان أكثر المواقع عرضة للالتهاب بالسلمونيلة هو الدم (٤٢% من المعزولات بالزرع) تبعها الجهاز الهضمي (٢٣,٥%) والجهاز الهيكلي (٢٢,٥%). التهاب السلمونيلة كان أكثر توارداً في المرضى ما دون الخامسة عشر من العمر. كانت معدلات الوفيات في مرضى حمج السلمونيلة ٢ر٢% (٣/١٣٩) بينما لم تكن هناك وفيات مرتبطة بأنواع أخرى من التهابات السلمونيلة. حدثت مقاومة لعقاري الأمبيسيلين والكوتريموكسازول في نسبة ٢٩% و ٢٤% من المعزولات بالزرع على التوالي، بينما نسبة ٠,٦% فقط كانت مقاومة لعقار سيفتراياكسون ومقاومة متوسطة بنسبة ١,٨% لعقار سيبروفلوكساسين.

الخلاصة: السلمونيلة سبب شائع للإصابة بالخمج والتهاب العظم والنقي في مرضى الخلايا المنجلية في منطقتنا. لا بد أن يشمل العلاج التخبري المضاد للجراثيم الجراثيم المرضة المحتملة بما في ذلك أنواع السلمونيلة.

المدونات الطبية السعودية ٢٣؛ ٦: ٣٥٨-٣٦٢

الخبرة الإقليمية في تقصي مرض الخلية المنجلية والاعتلالات الهيموغلوبينية الأخرى وعوز الإنزيم G6PD لدى المواليد

المقدمة: يعتبر تقصي مرض الخلية المنجلية والاعتلالات الهيموغلوبينية الأخرى وعوز الإنزيم G6PD لدى المواليد إحدى الوسائل الهامة لخفض معدلات الوفاة والمراضة في المناطق التي تكثر فيها هذه الحالات. وفيما يلي ملخص ٩ سنوات من الخبرة في تقصي هذه الحالات في مستشفى القطيف المركزي.

المرضى والطرق: أجريت فحوص على دم الحبل السري لتقصي مرض الخلية المنجلية والاعتلالات الهيموغلوبينية الأخرى وعوز الإنزيم G6PD لدى جميع المواليد في مستشفى القطيف المركزي. أجري رحلان كهربائي قلوي على جميع العينات. إذا تم التعرف على هيموغلوبين الخلية المنجلية فإنه يجرى رحلان كهربائي على هلام الأغار (أس الهيدروجين حامضي) للتأكد. استخدمت طريقة التقصي التألقي لفحص عوز الإنزيم G6PD. تولى أخصائي إرشاد المرضى الاتصال بوالدي الرضيع المصاب باعتلال هيموغلوبيني رئيسي، وأعيدت الفحوص للتأكد من تشخيص فقر الدم المنجلي أو التلاسيمية المنجلية. أما عائلات الرضع المصابين باعتلال هيموغلوبيني ثانوي وعوز الإنزيم G6PD فقد تم إبلاغهم بالنتائج في عيادة الأطفال الأصحاء.

النتائج: خلال الفترة من ديسمبر ١٩٩٢م إلى ديسمبر ٢٠٠١م تم تقصي ما مجموعه ٢٤٠١٢ مولودا: ٢١٨٥٨ (٩١,٠٣%) مولود سعودي و٢١٥٤ (٨,٩٧%) مولود غير سعودي. كانت أنماط الهيموغلوبين لدى السعوديين موزعة كما يلي: هيموغلوبين AF (طبيعي) لدى ٤٩,٥٢%، هيموغلوبين FS (مرض الخلية المنجلية) + هيموغلوبين FS Bart's (مرض الخلية المنجلية مع تلاسيمية ألفا) لدى ٢,٥٧%، هيموغلوبين AFS (الخلة المنجلية) + هيموغلوبين AFS Bart's (الخلة المنجلية مع تلاسيمية ألفا) لدى ٢١,١٤%، وتلاسيمية ألفا (على أساس أن هيموغلوبين Bart's ≥ ٢%) لدى ٣٥.٦٨%. وجد عوز الإنزيم G6PD لدى ٣٧,٠٢% و٢١,٢٧% من الذكور والإناث على التوالي. لم يحضر إلى عيادة أمراض الدم أو تعذر الاتصال ب ٤٨ (٨,٥%) مولود من أصل ٥٦٣ مولود سعودي تم تشخيص مرض الخلية المنجلية لديهم افتراضيا. تم تأكيد تشخيص فقر الدم المنجلي أو التلاسيمية المنجلية لدى ٥١٣ مريضا، ووجدت الخلة المنجلية لدى حالتين عند إعادة الاختبار. واجه أخصائي أمراض الدم مشاكل كثيرة، ووجد كثير من الآباء والأمهات صعوبة في حضور العيادة لأسباب اجتماعية اقتصادية، وكان من الصعب عليهم تقبل التشخيص الأولي وما تركه من تأثير على علاقة أحدهما بالآخر.

النتيجة: ما زالت الوقاية والتعرف المبكر على مرض الخلية المنجلية والاعتلالات الهيموغلوبينية الرئيسية الأخرى وعوز الإنزيم G6PD هي حجر الزاوية في تدبير هذه الأمراض. العوائق الرئيسية أمام نجاح تقصي الاعتلالات الهيموغلوبينية لدى المواليد هي مستوى التعليم ونقص القوة البشرية. نوصي بإدراج تقصي الاعتلالات الهيموغلوبينية وعوز الإنزيم G6PD ضمن البرنامج الوطني لتقصي قصور الغدة الدرقية في المنطقة الشرقية وتأسيس مركز خاص للاعتلالات الهيموغلوبينية رفيع المستوى في القطيف.

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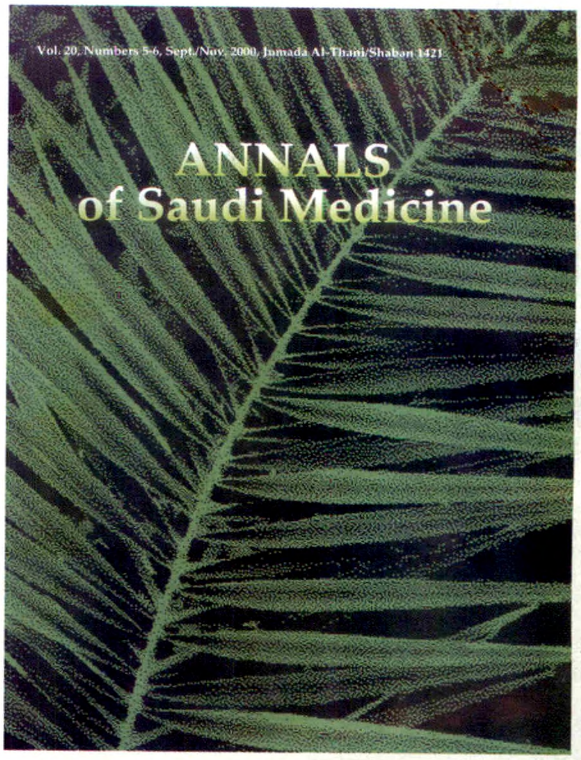

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فريق التحرير

جون كاثي، محرر أول
أورورا ب. جتريز، مساعدة التحرير
آنا فيرمينا ج. جارسيا، مساعدة التحرير

تصدر المدونات الطبية السعودية مرة كل شهرين عن مستشفى الملك فيصل التخصصي ومركز الأبحاث، ص.ب ٣٣٥٤ – الرياض ١١٢١١، المملكة العربية السعودية. يتم توزيع المدونات وإعداد الملخصات العربية بالتعاون مع د. زهير القاوي بواسطة موظفي إدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. جميع المراسلات والاستفسارات وطلبات الاشتراك ترسل إلى المحرر الأول، مكتب المطبوعات (ر.إ ٣٦). سعر الاشتراك ٥٠ ريال في السنة للأفراد، و١٠٠ ريال في السنة للمؤسسات.

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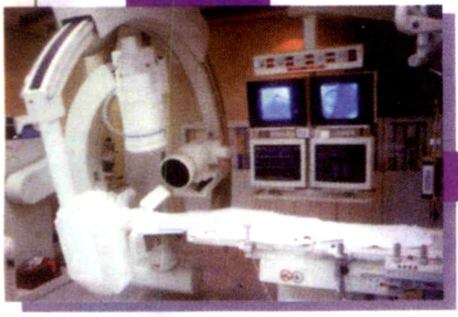

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